

# **Synthesis of Nitrogenous Heterocycles Using Transition Metal-Catalysed Cyclization Reactions**

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**Shazia Zaman**

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## ABSTRACT

This thesis addresses the use of two general methods involving transition-metal catalyzed cyclization for the synthesis of nitrogenous heterocycles. The amino-Heck reaction was applied to the synthesis of spiroimines, pyrroles and simple and amino acid-based imidazoles while ring-closing metathesis was applied to the synthesis of seven- and six-membered lactam analogues of cyclic urea HIV protease inhibitors. The lactams were further derivatized to epoxides, and to *cis*-diols using Sharpless asymmetric dihydroxylation.

*Chapter One* describes the significance of nitrogenous heterocycles in life and society with examples from peptidomimetics, synthetic and medicinal chemistry. The various approaches used in the design of peptidomimetics are then reviewed. The amino-Heck reaction and ring closing metathesis, used for the synthesis of nitrogenous heterocycles, are introduced briefly with an explanation of the catalytic pathways involved in these two processes.

*Chapter Two* gives a description of the role of palladium in organic and heterocyclic syntheses with applications to carbon-carbon and carbon-nitrogen bond formation. Palladium-catalyzed carbon-nitrogen bond formations are discussed in detail. The Amino-Heck reaction, an important new method for the formation of heterocycles from olefinic oxime derivatives, is then reviewed and discussed in terms of its applications towards the synthesis of various nitrogenous heterocycles.

*Chapter Three* describes the first domino-mode Amino-Heck reaction towards the synthesis of spirobicyclic and tricyclic imines. Cephalotaxine and its ester derivatives, harringtonine and homoharringtonine, have displayed powerful activity against chronic myelogenous leukaemia. 1-Azaspiro[4.4]nonane, which makes the core structure of Cephalotaxine, and its analogues **3.18a-d**, were synthesized by a domino Amino-Heck reaction of the dienyl ketone *O*-pentafluorobenzoyl oximes. The domino Amino-Heck

reaction of a trienyl ketone *O*-pentafluorobenzoyl oxime was also undertaken for the synthesis of a diastereomeric mixture of spirotricyclic imines **3.18g** and **19**.

*Chapter Four* extends the scope of the Amino-Heck reaction to the synthesis of trisubstituted imidazoles. Various derivatives of imidazoles **4.13a-c** were synthesised starting from simple non-peptide aldoximes. The generality of the reaction was further extended to the synthesis of optically-active  $\alpha$ -amino acid-based imidazoles **4.22a-c** from  $\alpha$ -amino aldoximes. The reaction proceeds with little or no racemization as determined by coupling of the (*S*)-Phe-based imidazole **4.22a** with (*S*)-*N*-Boc alanine to give a single diastereoisomer **4.24** (95% *de*, determined by  $^1\text{H}$  and  $^{13}\text{C}$  NMR). The C-terminal amino acid-based imidazoles have found applications as potential *cis*-amide bond isosteres in peptidomimetics. The reaction works well for the synthesis of both simple and amino acid-based imidazoles from olefinic derivatives of the respective *O*-pentafluorobenzoyl amidoximes.

*Chapter Five* describes a further application of the Amino-Heck reaction from propargylic type derivatives of ketoximes to the synthesis of 2,5-disubstituted pyrroles. Various domino processes, e.g. transmetallation, intermolecular Heck reaction and carbonylation with sequential treatment with alcohols, were attempted for termination of the living palladium(II) complexes that were generated from oxidative addition of palladium into the N-O bond of the oxime followed by triple bond insertion reactions. Termination under Amino-Heck reaction conditions gave the corresponding pyrroles, whereas the amino-Heck-carbonylation-termination with alcohols sequence led to the synthesis of 5-aryl-2-pyrroloesters.

*Chapter Six* presents a detailed overview of ring-closing metathesis. The development and functional group tolerance of ruthenium, molybdenum and other catalysts, and their use in the synthesis of peptidomimetics and non-peptidomimetics-based nitrogenous heterocycles are reviewed. Ring-closing metathesis from diene, ene-yne, ene-yne-ene and diyne precursors are discussed in detail. In addition, other miscellaneous applications of RCM are described.

*Chapter Seven* describes a versatile ring-closing metathesis approach to the synthesis of seven-membered lactam analogues of cyclic urea HIV protease inhibitors. The lactams **7.30**, **7.40** and **7.48** were synthesized in good to excellent yields and derivatization of the double bond of lactams to epoxides (**7.31**, **7.41** and **7.49** respectively) and diols [(**7.32** and **7.33**), **7.42** and **7.50** respectively] was carried out successfully. The *syn*-stereoselectivity of the N-*t*-Boc group was determined in the asymmetric dihydroxylation of the lactam **7.30**. The enhancement in the *syn*-directing effect of the N-*t*-Boc group by C-4 (*R*)-phenyl group in lactam **7.40** and C-7 (*S*)-benzyl group in lactam **7.48** was determined by the synthesis of a single diastereoisomer (**7.42** and **7.50**) from the corresponding lactam. The reinforcement of the *syn*-stereoselectivity by C-7 (*S*)-benzyl group of the lactam **7.48** was further confirmed from the synthesis of a single diastereoisomer **7.50** by carrying out the asymmetric dihydroxylation of **7.48** in the absence of ligands.

## ABBREVIATIONS

AD	Asymmetric dihydroxylation
$[\alpha]_D$	specific rotation
A-H	Amino-Heck
Boc	<i>tert</i> -butyloxycarbonyl
brs	broad singlet (in NMR)
BOP	benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
COSY	correlation spectroscopy
$\delta$	chemical shift
d	doublet (in NMR)
DCM	dichloromethane
dd	doublet of doublets (in NMR)
DIBALH	diisobutylaluminium hydride
DIEA	<i>N,N</i> -diisopropylethylamine
DMAP	4- <i>N,N</i> -dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
EA	ethyl acetate
EDCI	1-[3-(dimethylamino)propyl]-3-carbodiimide hydrochloride
EI	electronic impact ionisation (in mass spectrometry)
equiv.	equivalents
ES	electrospray ionisation (in mass spectrometry)
FTIR	fourier transform infrared
h	hour(s)
H	Hexane
HHT	homoharringtonine
HIV	human immunodeficiency virus
HMBC	heteronuclear multiple bond correlation (in NMR)
HOBT	1-hydroxybenzotriazole

HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single quantum correlation (in NMR)
Hz	hertz (in NMR)
<i>J</i>	coupling constant
LiHMDS	lithium bis(trimethylsilyl)amide
LRMS	low resolution mass spectrometry
m	multiplet (in NMR)
Micro.	microanalysis
min	minute(s)
NEM	<i>N</i> -ethylmaleimide
NMO	4-methylmorpholine- <i>N</i> -oxide
NMP	1-Methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
PE	petroleum ether (bp 50-70 °C)
ppm	parts per million
RCM	ring-closing metathesis
RCAM	ring-closing alkyne metathesis
RCEYM	ring-closing ene-yne metathesis
RCEYEM	ring-closing ene-yne-ene metathesis
rt	room temperature
s	singlet (in NMR)
t	triplet (in NMR)
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography

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## **DEDICATION**

I dedicate this piece of work to my two loving children HAIDER ZAMAN KHAN and  
MAMUNA ZAMAN KHAN.

# **CHAPTER ONE**

## **GENERAL INTRODUCTION**

## 1.1 Introduction

Many N-heterocyclic compounds occur naturally and their functions are often of fundamental importance to living systems: biochemical reactions that involve N-heterocyclic systems are important in many physiological processes, such as provision of energy, transmission of nerve impulses, sight, metabolism and transfer of hereditary information. The reason that nature utilises so many nitrogenous heterocyclic compounds lies in their remarkable properties. Nitrogen-containing heterocycles can behave like acids (the NH group of pyrroles), bases (the N group of pyridine), or be amphoteric (imidazoles). Another important property of N-heterocyclic compounds is their ease of coordination with metal atoms. This can be seen in natural compounds like haeme and chlorophyll, which are important components in photosynthesis and oxygen transport in plants and animals. N-heterocycles are also able to participate in hydrogen bonding. For example, polypeptide helical chains and the double helical structure of DNA are stabilized by such interactions. Due to these striking properties, N-heterocycles have found wide-spread applications as key components of a large number of biologically-active natural products. Examples include antibiotics such as penicillin and cephalosporin, alkaloids such as vinblastine, ellipticine, morphine and reserpine, and marine natural products like sceptrin and ageliferin and fungal natural product like cyclosporine A and FK506, all exhibiting interesting biological properties. However, synthetic N-heterocyclics have also found widespread use in pharmaceuticals as anticancer agents, analeptics, analgesics, hypnotics and vasopressor modifiers, in agrochemicals as pesticides, insecticides and herbicides, in material sciences as polymers, dyestuffs, photographic sensitizers and developers, antioxidants and vulcanization accelerators in the rubber industry.

The successful application of heterocyclic systems in these and many other areas, and their significance in applied chemistry, arise from their very complexity. This ensures numerous novel compounds with a range of physical, chemical and biological properties, displaying a

broad spectrum of reactivity and stability. A good deal of effort has, therefore, gone into the synthesis of this biologically diverse and important class of compounds. What follows is a detailed overview of the significance of heterocyclic systems in peptides and proteins.

## 1.2 N-Heterocycles in Peptides and Proteins

Peptides and proteins are a particularly important class of natural compounds, because of their role in a wide variety of processes that are fundamental to living organisms. Cellular membrane walls, supporting and protective tissues, and muscle fibres are among many examples of living structural materials made up of proteins. Twenty primary amino acids exist in nature, and each contains an amino group, a carboxylic acid and a sidechain group, R, attached to a central carbon (Figure 1.1a). Amino acids are linked together by condensation of the amino group of one amino acid with the carboxyl group of another to form an amide or peptide (CONH) bond (Figure 1.1b). Proteins are derived from the combination of the twenty primary amino acids to give an infinite number of possible sequences within the polypeptide chain.

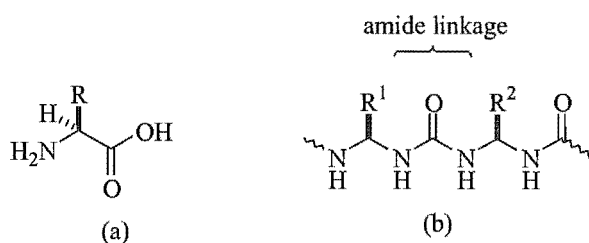


Figure 1.1: a) general structure of the primary amino acid. b) a peptide chain joined by amide linkage.

The common amino acids differ only in the nature of the R groups. Histidine (1.1), tryptophan (1.2) and proline (1.3) are among the primary amino acids whose sidechains are derived from N-heterocyclic residues, are depicted in Figure 1.2.

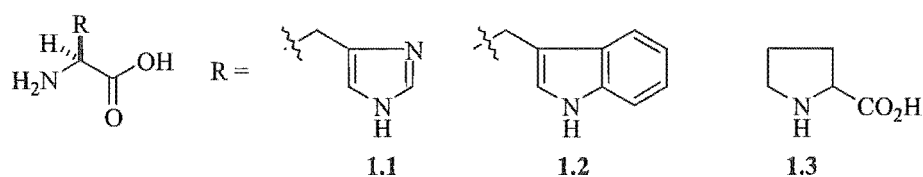


Figure 1.2: Heterocycle-based primary amino acids.

Several additional non-protein amino acids have evolved from the diverse metabolism of plants and microorganisms, some of which are biochemically important. For example, histamine 1.4, derived from histidine by enzymatic decarboxylation, is the cause of allergies in mast cells. It also dilates blood vessels, increases the permeability of capillaries, and constricts bronchial air passages (Figure 1.3). Similarly, serotonin (1.5), derived from tryptophan by enzymatic hydroxylation at C-5 followed by decarboxylation, acts as a neurotransmitter and a regulator (Figure 1.3).

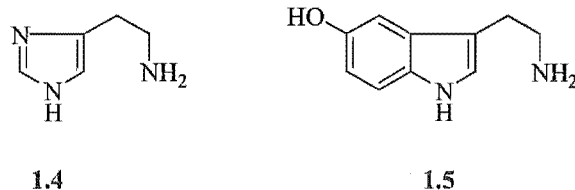
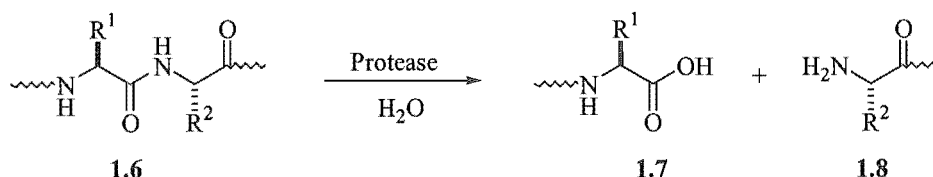


Figure 1.3: Biochemically important derivatives of histidine and tryptophan.

Enzymes, nature's biocatalysts, are of crucial importance in chemical and physiological processes in organisms. The tertiary structure of an enzyme defines clefts, pockets and/or trenches on the surface. The active site of an enzyme is a cleft into which a specific substrate enters. The imidazole ring of histidine (1.1) is often associated with catalytic activity because of its acid base properties and ability to participate in hydrogen bonding. The high basicity of the imidazole ring of histidine enables it to form strong hydrogen bonds and also to abstract a proton from an acid, such as water or an alcohol. The imidazole ring can catalyze a nucleophilic addition to a carbonyl group through 'general base

catalysis'. Such catalysis is best illustrated by the hydrolytic cleavage of a peptide bond in a protein or polypeptide by a class of enzymes named proteases (see Scheme 1.1).



Scheme 1.1: Hydrolysis of the peptide **1.6** by a protease to give fragments **1.7** and **1.8**.

A histidine residue is a constituent of the active site of many enzymes, e.g. serine proteases, where it plays a key catalytic role (Fig.1.5). The mechanism of amide bond hydrolysis by serine proteases involves a catalytic triad of amino acids denoted as Ser195, His57 and Asp102 (Figure 1.5). The numbers 195, 57 and 102 represent the position of the corresponding amino acid in the polypeptide chain.<sup>1</sup> Figure 1.4 illustrates the mechanism of a serine protease catalyzed hydrolysis of a peptide bond.

The nucleophilicity of the hydroxyl group of Ser195 is enhanced by charge transfer from His57 and Asp102. Attack on the carbonyl group of the substrate **1.6** then occurs to form a tetrahedral complex **1.9**. The oxyanion of **1.9** is stabilized by hydrogen bonding to NH groups in an active site region termed the 'oxyanion hole'. The complex **1.9** is transformed to an acyl intermediate **1.10** along with the formation of the C-terminal fragment **1.8**. Hydrolysis of **1.10** by an active site water molecule then occurs with the release of N-terminal fragment **1.7** and regeneration of the catalytic triad (see Figure 1.4).

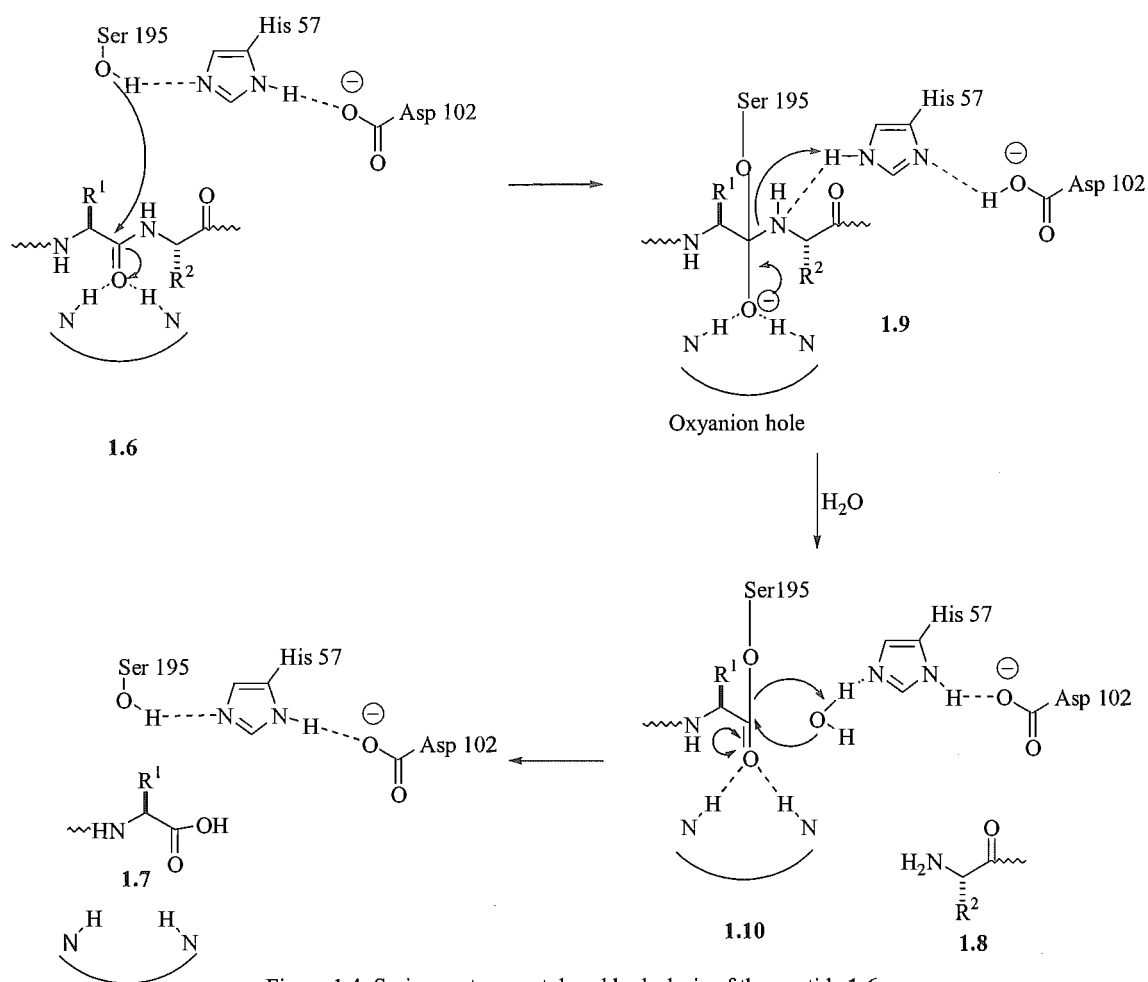


Figure 1.4: Serine protease catalyzed hydrolysis of the peptide 1.6.

Serine proteases are involved in a large number of physiological processes such as digestion and blood clotting, peptide hormone processing, fertilization, cell destruction and defense mechanisms.

### 1.3 Peptidomimetics<sup>2</sup>

The use of peptides as drugs is problematic due to their poor pharmacological properties such as low metabolic stability, vulnerability of the peptide bonds to hydrolysis, poor pharmacokinetics and poor oral bioavailability. Thus, a potent peptide may be active *in*

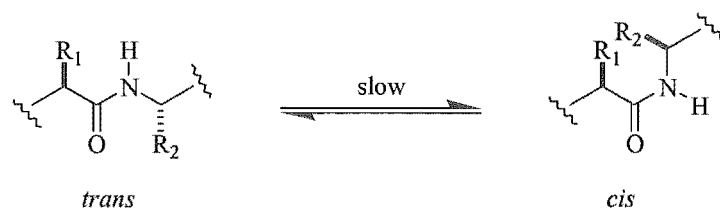


*vitro*, but not *in vivo* because of the above mentioned reasons. In order to circumvent these problems, considerable efforts have been invested in modification or non-peptide surrogates of biologically active peptides. These surrogates are referred to as peptidomimetics.

Peptidomimetics are designed on the basis of the conformational, topochemical and electronic properties of a native peptide and its receptor.<sup>3</sup> The design of a peptidomimetic as a potential bioactive substance, therefore, is of crucial importance and depends on two main structural factors; a favourable conformation with respect to spatial position of the active site, and the placement of certain structural elements in the defined positions so that the desired interactions can occur. What follows here is a discussion of various strategies that are usually employed in peptidomimetics design.

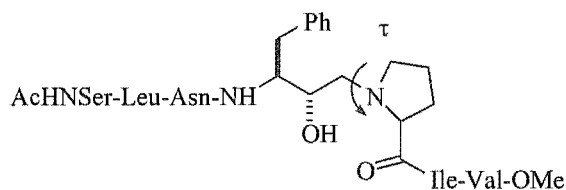
### 1.3.1 Conformational Restriction

A key principle in peptidomimetics design is the formation of conformationally-restricted ligands which mimic the bioactive conformation of the native peptide. The required bioactive conformation can be stabilized by incorporation of additional structural elements to enforce rigidity. The introduction of these rigid structural features in defined positions increases its affinity by lowering the entropy cost exhibited by a peptidomimetic upon binding to a receptor. Conformational restriction is always achieved by fixing a peptide bond into a *cis* or *trans* geometry. The pioneering research by Pauling and Corey on the structure of peptides and proteins revealed that the peptide bond is rigid and planar such that the H atom attached to the nitrogen is always *trans* to the carbonyl group due to the partial double bond character of the amide bond. The rate of interconversion between the *cis* and *trans* geometries is slow as a result of limited rotation about the amide bond (Scheme 1.2).



Scheme 1.2

The conformation of the amide bond, therefore, is of crucial importance to the binding of a peptide-based ligand to a receptor. An example is the Phe-Pro cleavage site in the substrates of HIV protease, a site distinct to retroviral proteases. Initial studies of HIV protease suggested that a *cis*-conformation was preferred at this position in substrates that bind in the active site of the enzyme. This resulted in the development of the potent HIV protease inhibitor JG-365 (**1.11**), a compound that contains a modified peptide bond to include a hydroxyethylamine isostere in place of the key phenylalanine residue<sup>4</sup> (Figure 1.5).

Figure 1.5: Hydroxyethylamine-based HIV Protease inhibitor JG-365 (**1.11**).

X-ray crystal studies of **1.11** bound to HIV protease<sup>5</sup> showed that the inhibitor binds to the active site in a pseudo-*cis* conformation about the C-C bond adjacent to the proline residue. The torsion angle about this bond is 11°, indicating the conformation to be essentially planar. However, while JG-365 is a potent inhibitor *in vitro*, it fails to inhibit HIV protease in cellular assays due to its peptide character. What follows is a discussion about the various approaches that have been used to develop conformational restriction in a peptidomimetic.

### 1.3.1.1 Introduction of Conformation-Stabilizing Rings

A classical approach in the design of peptidomimetics is the introduction of conformation-stabilizing rings. The introduction of rigid rings into a peptide molecule can improve the potency by locking the ligand in a preferred bioactive conformation, thus enhancing its activity for its associated receptor molecule (e.g. an enzyme active site). The ring can be incorporated within a single amino acid residue, e.g. **1.12**<sup>6</sup> and **1.13**,<sup>7</sup> or between two<sup>8,9</sup> or more amino acid residues (**1.14** & **1.15**), as shown in Figure 1.6.

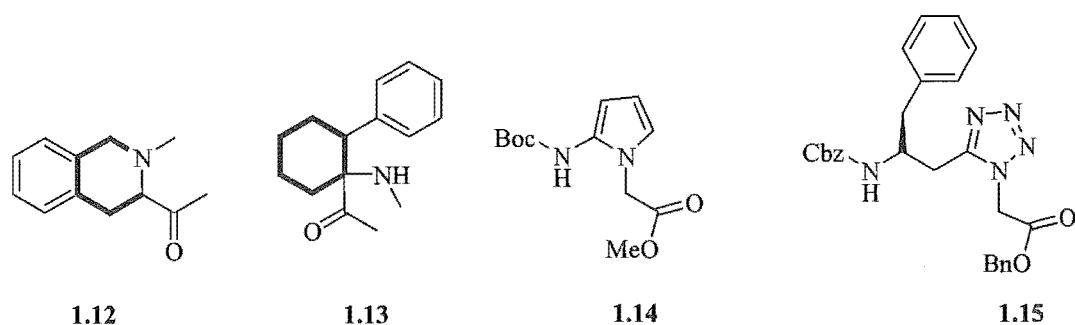


Figure 1.6: Some bridged amino acids.

Aromatic N-heterocycles (e.g. pyrroles, imidazoles and tetrazoles) have commonly been used to get the preferred *cis* conformation of the peptide bond. Research in this laboratory has focussed on the synthesis of different heterocycle-based amino acids that stabilize the *cis* geometry of the amide bonds. Abell *et al.* have reported the stereoselective synthesis of 1,2-disubstituted pyrrole mimetics (e.g. **1.14**, see Figure 1.6) in which a peptide bond is locked into a *cis* geometry by a planar aromatic pyrrole ring.<sup>8</sup> The same author and co-workers have also reported  $\alpha$ -methylene tetrazole-based dipeptidomimetics as illustrated by compound **1.15**<sup>9</sup> in Figure 1.6.

### 1.3.2 Modification of the Side Chains of Amino Acid Residues

A well-known strategy in peptidomimetics design is to modify the side chains of natural amino acid residues to give unnatural derivatives. Compounds **1.16** and **1.17** are examples of constrained mimetics of phenylalanine (see Figure 1.7) that have been incorporated into potent peptidomimetics ligands of the angiotensin II receptor.<sup>10</sup> Another example involves tyrosine analogue **1.18**, whereby the introduction of methyl groups at the 2', 6', and  $\beta$ -positions hinders the rotation about the  $C_\beta$ - $C_\gamma$  bond (Figure 1.7).<sup>11</sup> This has been shown to favour the formation of bioactive conformations in peptides (methionine-enkephalin)<sup>11</sup> and has been used to study the effects of restricted rotation of the peptide bond in peptide-protein complexes (e.g. oxytocin and neurophysin).<sup>12</sup>

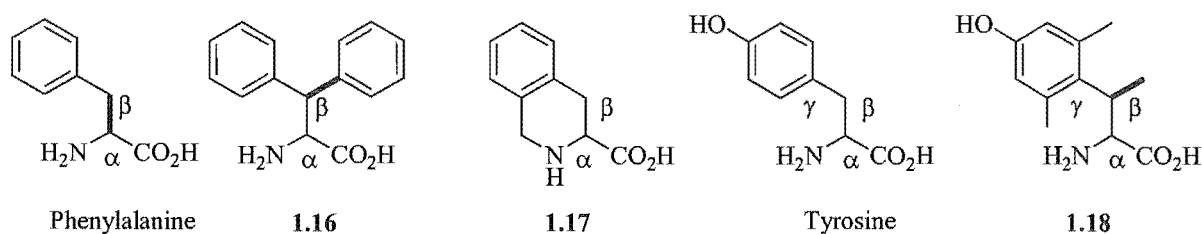


Figure 1.7: Sidechain modified amino acids.

### 1.3.3 Modification of the Peptide Backbone

A modification in the peptide backbone usually means the exchange of sterically- or electronically-equivalent structural units and the introduction of additional structural fragments.<sup>13</sup> These modifications bring a tremendous change in the peptide characteristics, such as proteolytic stability, while still retaining the key steric and electronic characteristics. The most common modifications are listed in Table 1.1.

Table 1.1: General modifications of a peptide backbone

NH	R CH	CO
— O —	— N —	— CS —
— S —	— C-R —	— CH <sub>2</sub> —
$\begin{array}{c} \text{O} \\ \parallel \\ \text{— CH}_2 \text{—} \end{array}$	— BH <sup>+</sup> —	— SO <sub>n</sub> —
	alkyl bora	thio reduced n = 1,2
		— P=O(OH) —
		— B(OH) —

Studies in this laboratory have shown that the phenylalanine-based inhibitor **1.15** (Figure 1.8) constrains the peptide backbone to adopt a similar conformation to that of JG-365 (**1.11**) by incorporation of a tetrazole moiety as a *cis*-amide bond isostere. The tetrazole moiety constrains the peptide such that the torsion angle about the C-tetrazole bond is approximately 13°, which is very close to the equivalent C-C bond in the bioactive conformation of **1.11**. Consequently, compounds of type **1.15**, that contain a modified tetrazole backbone, have been found to be good inhibitors of HIV protease.<sup>8</sup> Similarly, the amide bond can also be locked into a *cis* geometry by the incorporation of an imidazole ring to make biologically important peptidomimetics of type **1.19**.

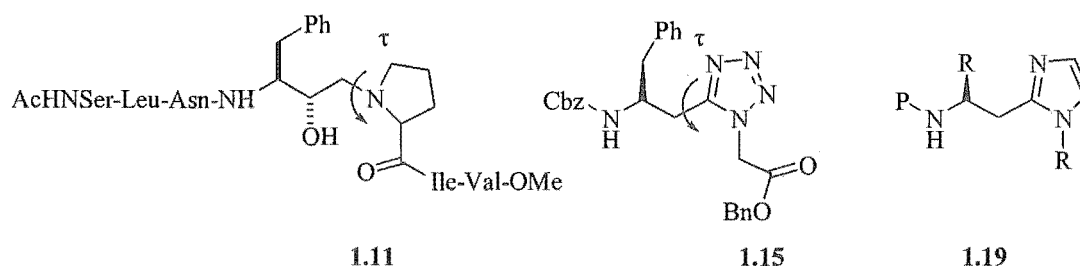


Figure 1.8: Introduction of conformational restriction by the incorporation of a tetrazole or imidazole ring.

Another example is modification of the backbone of the tetrapeptide Cys-Val-Ile-Met (**1.20**, see Figure 1.9), that inhibits Farnesyltransferase (a heterodimeric Zn metalloenzyme) *in vitro* ( $IC_{50} = 340$  nM). Inhibition of this enzyme is an important target in cancer therapy.<sup>14</sup> Unfortunately, **1.20** is inactive in whole cell assays due to its poor membrane permeability and metabolic stability, features typical of peptides. Therefore, to improve its inhibitory activity, the peptide backbone was modified by replacing Val-Ile-Met with a conformationally restricted 4-amino-3'-carboxy phenyl group to give **1.21**.

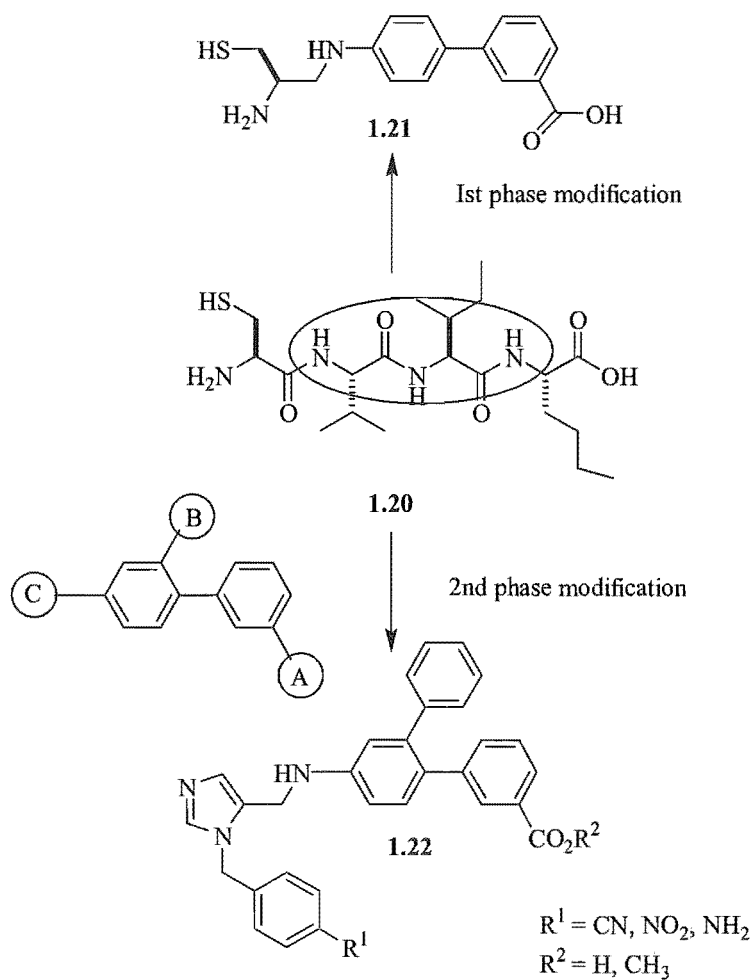


Figure 1.9: Modification in the peptide backbone of **1.20** to give better inhibitors, **1.21** and **1.22**.

Further modification by replacement of the 4-amino-3'-carboxy phenyl group with a biphenyl moiety led to an improvement in the inhibitory activity of the Farnesyltransferase inhibitors.<sup>15</sup> In particular, the replacement of the cystein residue of **1.20(C)** with an *N*-benzyl substituted imidazole ring to give the inhibitor **1.22** ( $IC_{50} = 1-10 \mu M$ ) resulted in a substantial increase in the whole cell inhibitory activity. This is attributed to the increased binding ability of the inhibitor **1.22** (through the imidazole group) to the  $Zn^{2+}$  ion in the active site of the enzyme.<sup>15</sup>

## 1.4 Cyclic Peptidomimetics

The incorporation of bridging rings is another strategy for the design of conformationally constrained peptidomimetics. An example is the *de novo* design of cyclic urea inhibitors of HIV protease. Based on the  $C_2$ -symmetry of the HIV protease dimer, peptidomimetics-based inhibitors of type **1.23**, containing a diol moiety, were developed and found to be good inhibitors of HIV protease (Figure 1.10a). However, diols of this type experienced the characteristic drawbacks of peptides, i.e. poor solubility and poor bioavailability. To reduce the peptidic character of the HIV protease inhibitors, Lam *et al.*<sup>16</sup> utilised a 3D computer programme to develop the cyclic structures shown in Figure 1.10. The first model structure was a phenyl-ring based structure (Figure 1.10b), but later on this was rejected as a phenyl ring might not position all parts of the inhibitor properly. This was replaced by a cyclohexanone ring (Figure 1.10c) with the carbonyl oxygen as a structural water mimic. The six-membered ring was enlarged in the next step to a seven-membered ring cyclic urea scaffold containing a diol moiety, as the SAR studies of linear inhibitors containing diols were found to show better potency than the corresponding mono-ol inhibitors. The final synthetic target was a cyclic urea scaffold to replace the structural water molecule, as well as the basic structural motifs necessary to bind in the active site of the HIV protease (Figure 1.10d). This resulted in the development of cyclic urea analogues of HIV protease inhibitors. The subsequent synthesis of cyclic ureas led to potent and highly bioavailable

HIV protease inhibitors e.g. DMP 323 (Figure 1.10d). A number of cyclic urea-based HIV protease inhibitors have since been synthesized and have proved to be better inhibitors by exhibiting high bioavailability and good pharmacokinetics in humans.<sup>16</sup> Figure 1.10e illustrates the enhanced H-bonding interactions to the active site residues, resulting from the cyclic nature of the urea mimic. Compounds of this type are discussed further in chapter seven.

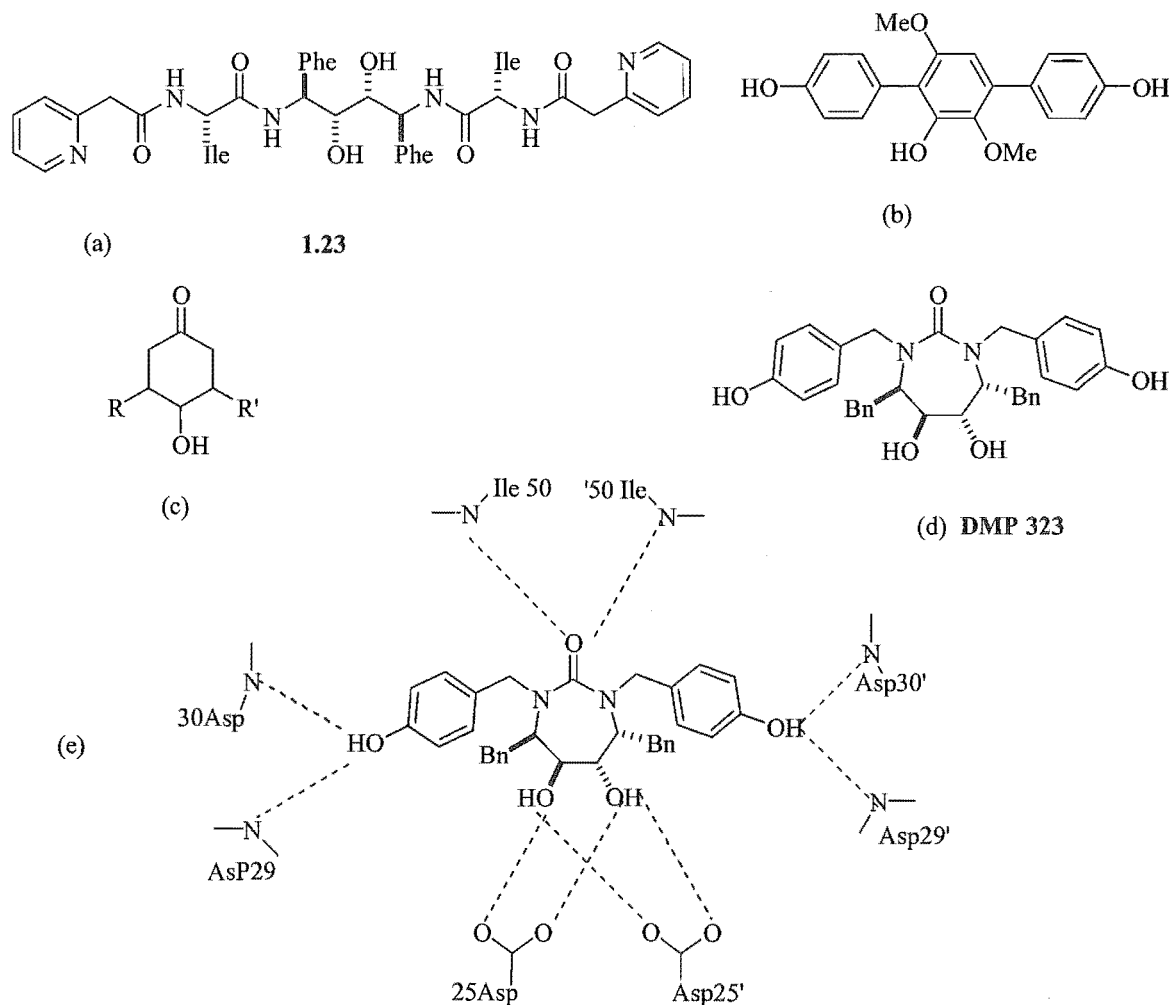


Figure 1.10: Steps (a-d) involved in the design of cyclic urea inhibitors of HIV protease. (e) enhanced H-bonding of **DMP 323** with HIV protease inhibitor.



Examples of the use of cyclic amino acids are found in the seven-membered cyclic lactams **1.24-1.26** which dimerize in non-polar solvents to give  $\beta$ -turn peptide mimetics<sup>17</sup> (Figure 1.11).

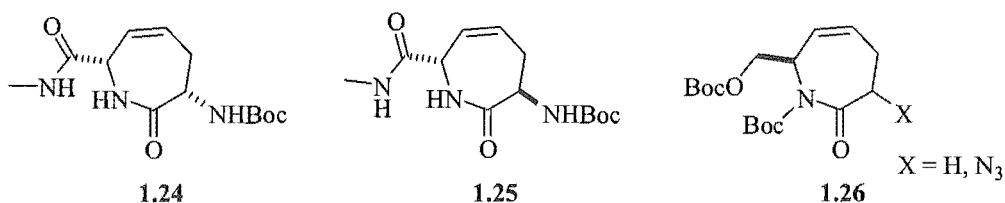


Figure 1.11: Some  $\beta$ -turn inducing cyclic amino acids.

$\beta$ -Peptides (derived from  $\beta$ -amino acids) are biologically- and structurally-important compounds. Unlike peptides derived from  $\alpha$ -amino acids,  $\beta$ -peptides exhibit high resistance to peptidase hydrolysis and have the ability to adopt stable secondary structures such as helices, sheets, and turns. Research carried out in this laboratory has resulted in the synthesis of cyclic 5-7 membered  $\beta$ -Peptides **1.27-1.29** (Figure 1.12) via RCM methodology which has been discussed in section 1.5.2.<sup>18</sup> What follows here is a discussion about the applications of heterocyclic compounds in pharmaceuticals and other fields.

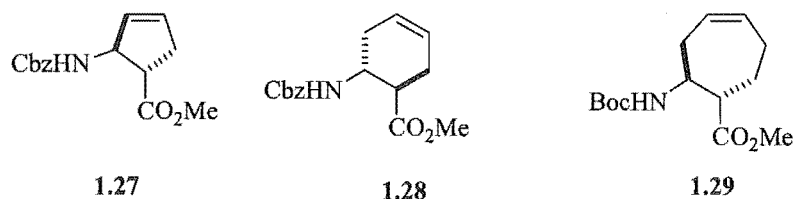


Figure 1.12: Cyclic  $\beta$ -peptidomimetics.

## 1.5 Applications of N-Heterocycles in Medicine and Other Fields

Besides their abundance in nature, N-heterocyclic compounds are of importance as building units in pharmaceuticals. Examples include allopurinol **1.30** (gout therapeutic),<sup>19</sup> sildenafil

1.31 (inhibitor of type V cGMP phosphodiesterase, Viagra), tubersidin 1.32 (anticancer agent), abacavir 1.33 (anti HIV agent), acyclovir 1.34 (antiviral agent for the treatment of Herpes) and eprosartan 1.35 (antihypertensive agent) (Figure 1.13). Heterocyclic nitroimidazole pharmaceuticals, such as metroindazole 1.36 and tinidazole 1.37, work as magic bullets for the treatment of trichomonas infections (see Figure 1.13).

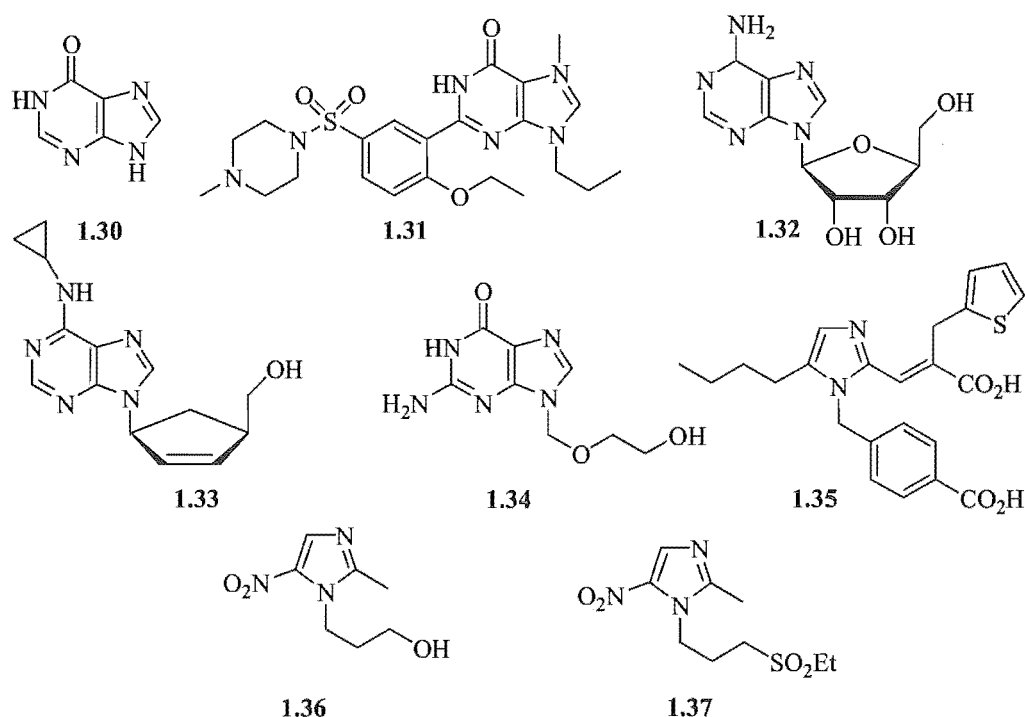


Figure 1.13: Heterocycle-based pharmaceuticals.

In addition, N-heterocyclic compounds like  $\beta$ -lactams make up the core structure of antibiotics, such as penicillin G 1.38 and Cephalosporin C 1.39.  $\delta$ -Lactams (e.g. 1.40<sup>20</sup> & 1.41<sup>21</sup>) have found applications as HIV protease inhibitors (Figure 1.14).

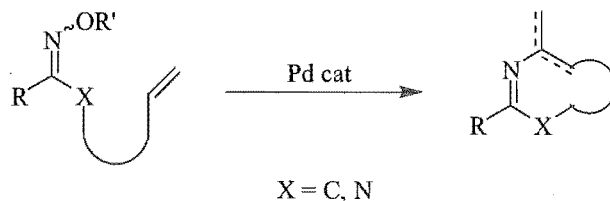


## 1.6 Metal-Catalyzed Ring Closure as a General Method for the Synthesis of Heterocycles

Transition metal catalyzed reactions offer some of the most attractive methodologies for synthesizing heterocycles. They allow the convenient construction of complex molecules under mild conditions. A number of methods involving transition metal catalyzed synthesis of N-heterocycles have been reported and reviewed.<sup>22</sup> The two general methods used in this thesis for the preparation of peptide and non-peptide N-heterocyclic compounds are introduced briefly in the following two subsections.

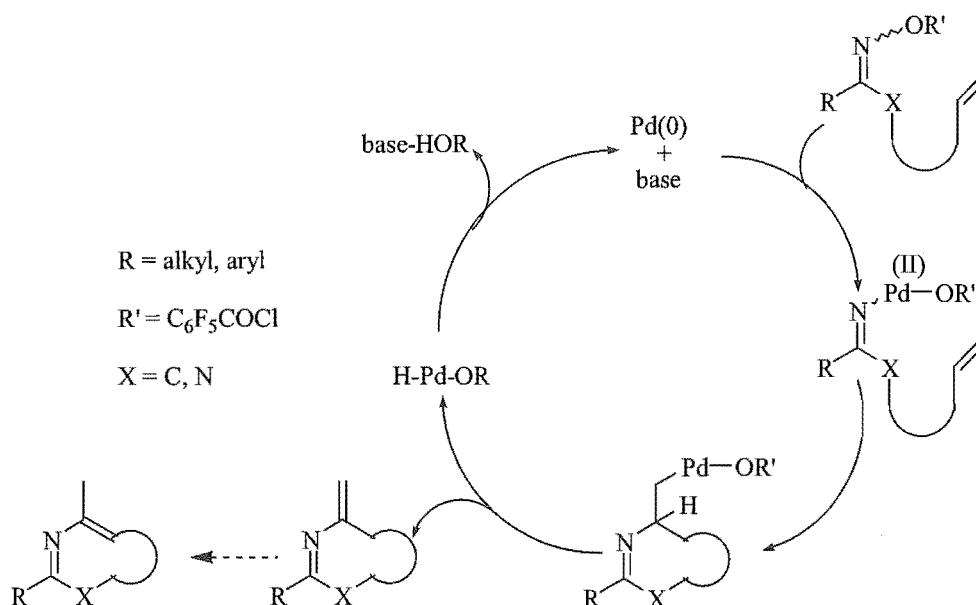
### 1.6.1 Palladium-Catalyzed Amino-Heck (A-H) Cyclization from Olefinic Oximes

The amino-Heck (A-H) reaction, developed recently by Narasaka *et al.* has emerged as an attractive and powerful tool for the synthesis of a variety of N-heterocycles.<sup>23</sup> The reaction involves an intramolecular cyclization of an olefinic oxime in the presence of a palladium(0) catalyst (e.g.  $\text{Pd}(\text{PPh}_3)_4$ ), a base, and a polar solvent, such as DMF (Scheme 1.3). The reaction proceeds in a fashion very similar to an intramolecular version of the Mizoroki-Heck reaction.<sup>24</sup> The reaction, which is usually carried out at mild temperatures with various derivatives of oxime starting materials bearing electron-rich and electron-deficient olefins, works in the presence and/or absence of additives.<sup>25</sup>



Scheme 1.3. Palladium-catalyzed amino-Heck reaction.

The utility of this reaction lies in the generation of an alkylidenepalladium(II) aminyl intermediate which could be used for the synthesis of various nitrogenous heterocycles. A schematic representation of the mechanism is illustrated in scheme 1.4.



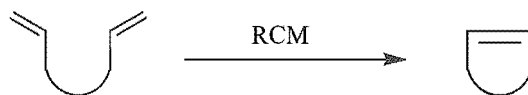
Scheme 1.4: Catalytic cycle of the amino-Heck reaction.

The pioneering work in this area by Tsutsui *et al.* revealed that the geometry of the oxime does not affect the reaction: pyrrole derivatives from both *E* and *Z* oximes have been prepared in very good yields.<sup>20</sup> The reaction can also be carried out from both terminal and branched olefinic oxime derivatives. A more detailed discussion on A-H cyclization will be described in chapter 2 of the thesis.

### 1.6.2 Ring-Closing Metathesis (RCM)

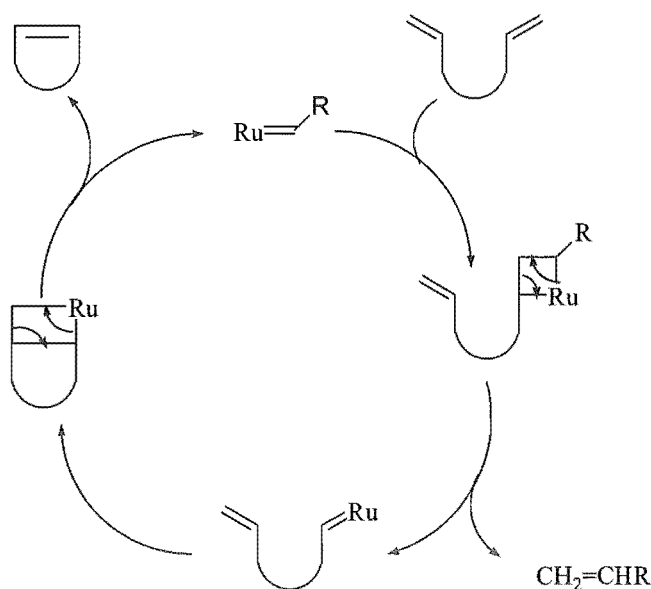
Ring closing metathesis (RCM) has emerged as a new and powerful technique over the past decade for the synthesis of a wide range of peptide and non-peptide heterocycles and carbocycles. The power of this reaction lies in its ability to form a ring from a molecule

containing two olefins under mild reaction conditions and with good functional group tolerance. The reaction involves joining together two carbon-carbon double bonds, in the presence of a transition metal catalyst to form a new carbon-carbon double bond (Scheme 1.5).



Scheme 1.5: Ring Closing Metathesis reaction.

The reaction can be carried out at room temperature and in a variety of solvents. A number of stable, well-defined and functional group tolerant metal carbene catalyst systems allow a wide scope of syntheses. The catalytic cycle involved in the reaction is depicted in Scheme 1.6 below.

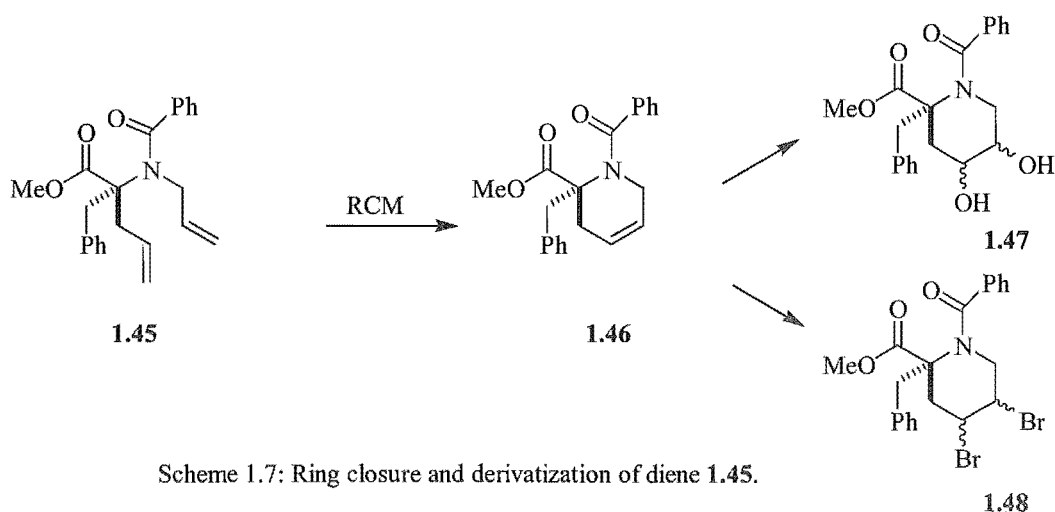


Scheme 1.6: Catalytic cycle of the Ring Closing Metathesis of dienes.

The most commonly used catalysts for RCM are the ruthenium-based compounds developed by Grubbs *et al.*<sup>26</sup> and molybdenum-based compounds developed by Schrock *et al.*<sup>27</sup> Ruthenium-based catalysts are usually preferred over the molybdenum-based catalysts which are sensitive to air, moisture and other impurities.

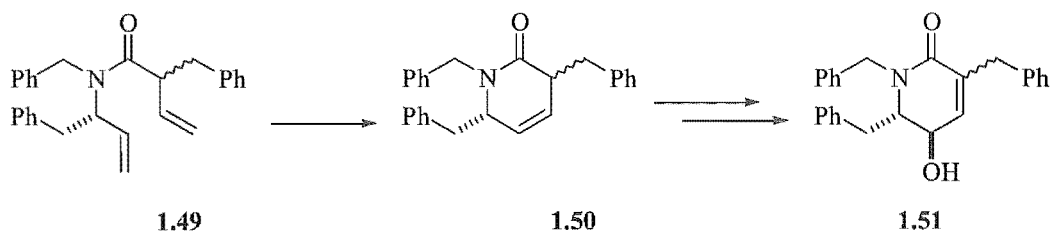
RCM of nitrogen-containing compounds, with applications towards the preparation of heterocycles, alkaloids and peptidomimetics, has been the focus of much research and has recently been reviewed.<sup>28</sup> Research in this laboratory has focused on the synthesis of constrained peptidomimetics and carbocycles from  $\alpha$ - and  $\beta$ - amino acids.

Recently, Gardiner *et al.* synthesized the  $\alpha,\alpha$ -disubstituted tetrahydropiperidine mimic **1.46** from the diene **1.45** using RCM methodology and successively derivatized it to the diastereoisomeric mixture of diols (**1.47**) and dibromo derivatives (**1.48**),<sup>29</sup> as illustrated in Scheme 1.7.



Scheme 1.7: Ring closure and derivatization of diene **1.45**.

Humphries and co-workers synthesized the  $\delta$ -lactam **1.50** from the diene linker **1.49** and transformed it to allylic alcohol **1.51** (as depicted in Scheme 1.8),<sup>30</sup> analogues of which have been reported to be inhibitors of HIV protease.<sup>21</sup>



Scheme 1.7: Ring closure by RCM and derivatization of diene 1.49.

A more detailed discussion about RCM, catalysts used in RCM, and its applications in organic synthesis will be presented in chapter 6.

## 1.7 Research Work described in this Thesis

This thesis covers two general areas that utilise A-H and RCM chemistry for the synthesis of biologically-important N-heterocyclic compounds: chapters 2-5 cover A-H chemistry for the synthesis of N-heterocyclic compounds, and chapters 6 and 7 cover RCM-based syntheses.

The next chapter describes a more detailed specific background to the synthesis of N-heterocycles from olefinic oximes by using the palladium-catalyzed A-H cyclization reaction. The extension of this synthetic methodology to various types of N-heterocycles is also presented.

Chapter 3 describes the synthesis of spiro bicyclic imines from dienyl oxime precursors. 1-azaspiro[4.4]nonane, the base skeleton of the biologically active alkaloid cephalotaxin, and its synthetic analogues, have been prepared from dienyl ketoxime derivatives using the A-H reaction. This methodology has also proven to work in a domino manner for the synthesis of tricyclic spiroimines.



Chapter 4 describes the extension of the same methodology to the synthesis of imidazoles. Applications described involve the preparation of aliphatic and  $\alpha$ -amino acid based imidazoles (as amide bond replacements) from aliphatic and  $\alpha$ -amino aldoxime precursors. The reaction proceeds well without racemization of the stereocentre of the starting  $\alpha$ -amino aldoxime.

Chapter 5 highlights the synthesis of pyrrole derivatives by A-H cyclization of propargyl type derivatives of ketoximes. Several attempts were made to terminate the living alkenyl palladium(II) complexes by different methods involving the use of organometallic reagents, intermolecular Heck reaction and carbonylation-termination with alcohols. The A-H/carbonylation-termination via alcohols sequence was applied to the synthesis of 2,5-disubstituted pyrroles.

Chapter 6 provides an overview of olefin metathesis and its various types. In particular, a detailed introduction about the RCM technique, the different catalysts used in RCM (as well as their functional group tolerance capability), and its various applications to peptide and non-peptide N-heterocycles are described.

Chapter 7 of the thesis presents a versatile and convenient ring-closing metathesis approach to the preparation of  $\alpha$ -amino acid-based seven-membered lactams, and their derivatization to diols (using Sharpless asymmetric dihydroxylation reactions), and to epoxides. The RCM/dihydroxylation sequence allows access to diol-containing lactam analogues of cyclic ureas, which could prove to be potent HIV inhibitors.

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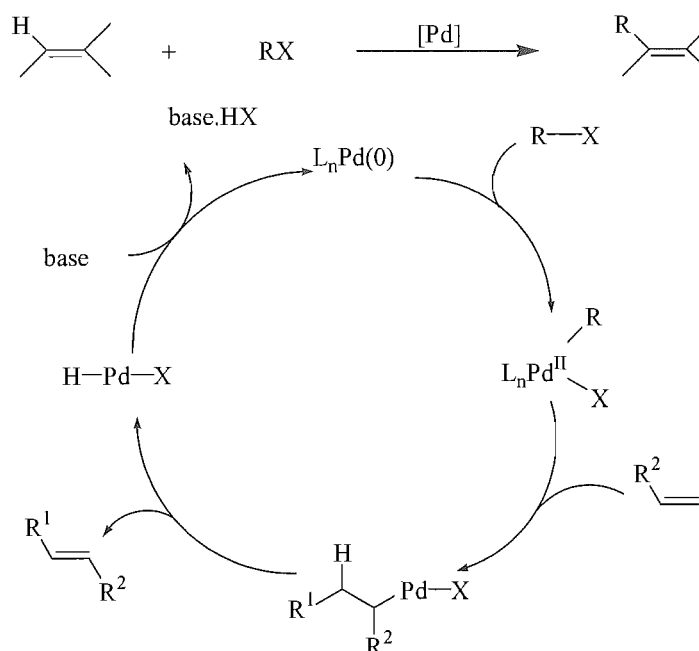
## **CHAPTER TWO**

### **PALLADIUM IN ORGANIC SYNTHESIS: APPLICATION TO C-C AND C-N BONDS SYNTHESES**

## 2.1 Introduction

Palladium chemistry has undergone considerable progress in the past three decades in the field of organic synthesis.<sup>1</sup> Organopalladium complexes have been used extensively in the recent development of efficient industrial processes<sup>2</sup> because of the stability, low toxicity and the ability of palladium to exist in a variety of oxidation states. Common examples of palladium catalysts are the air stable complex dichlorobis(triphenylphosphine)palladium(II)  $[\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]$  and the air sensitive complex tetrakis(triphenylphosphine)palladium(0)  $[\text{Pd}(\text{PPh}_3)_4]$ . The actual catalytic species appears to be 'bis(triphenylphosphine)' palladium(0)  $[\text{'Pd}(\text{PPh}_3)_2\text{'}]$ ,<sup>3</sup> or some other *in situ* generated analogue; they are strictly defined as the 'pre-catalysts'.

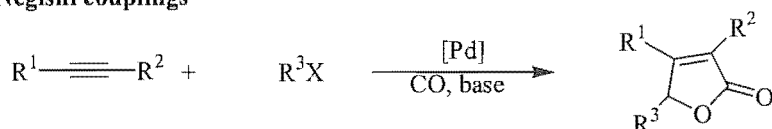
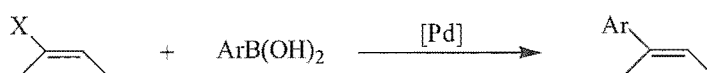
One of the major contributions of palladium catalysts is the formation of C-C bonds through coupling reactions. The most commonly used reaction for C-C bond formation is the Mizoroki-Heck reaction concurrently reported by Mizoroki<sup>4a</sup> and Heck<sup>4b</sup> in the early 1970s. The Mizoroki-Heck reaction mainly involves the fundamental reactions of organometallic chemistry i.e., oxidative addition, olefin insertion,  $\beta$ -hydrogen elimination and reductive elimination. The mechanism of the reaction is illustrated in Scheme 2.1.



Scheme 2.1: Catalytic cycle of Mizoroki-Heck reaction.

The first step involves the oxidative addition of an organic halide to form an alkylpalladium complex, which then undergoes alkene insertion to form a second alkylpalladium(II) intermediate. *Syn*-elimination of  $\beta$ -hydrogen from the second palladium intermediate affords a new alkene molecule and a palladium hydride. Reductive elimination of palladium(II) to palladium(0) occurs from palladium hydride to complete the catalytic cycle.

Other principal palladium-catalyzed reactions<sup>5</sup> include Negishi coupling, Suzuki coupling, Stille coupling, Sonogashira coupling and the Tsuji-Trost reaction, as summarized in Scheme.2. 2.

**Heck Reaction****Negishi couplings****Suzuki couplings****Stille couplings****Sonogashira couplings****Tsuji-Trost Reaction**

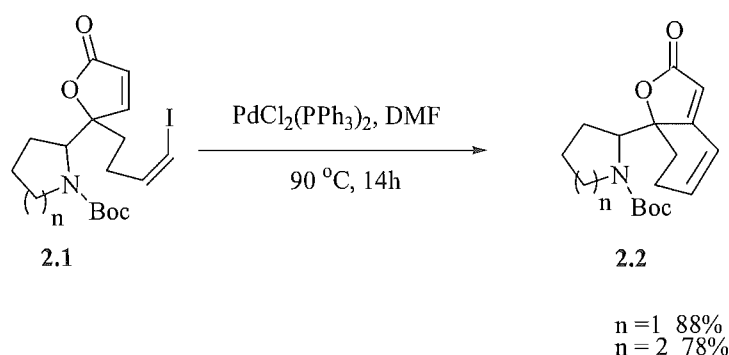
Scheme 2.2: Palladium-catalyzed reactions.

## 2.2 Palladium in Heterocyclic Chemistry

Palladium chemistry involving heterocycles has its unique characteristics arising from the heterocycles' inherently different properties from carbocycles. A novel example that illustrates the striking difference between a carbocyclic and heterocyclic arene is the heteroaryl Heck reaction (inter- or intramolecular), which occurs onto a heteroaryl substrate. Heterocycles, including thiazoles, oxazoles, imidazoles, pyrroles and indoles are excellent substrates for intermolecular Heck reactions, whereas, examples of carbocyclic substrates are rare.<sup>6</sup> In contrast, intramolecular Heck reactions of carbocyclic substrates have been well-precedented.<sup>7</sup>

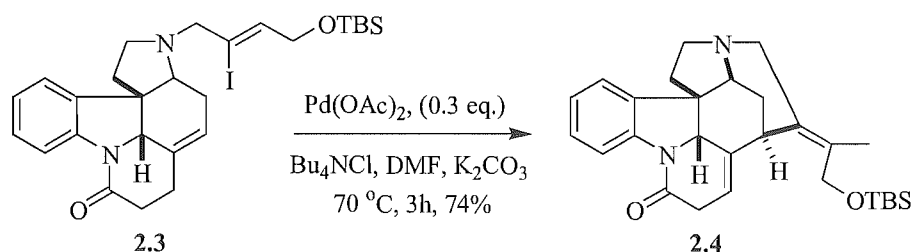


In fact, the intramolecular version of the Heck reaction has been extremely fruitful, enabling elegant total synthesis of complex molecules.<sup>8</sup> An intramolecular Heck reaction has been used as a key step in the synthesis of (-)-allonorsecurinine and securinine<sup>9</sup> (**2.2**) from a vinyl iodide (**2.1**, Scheme 2.3).



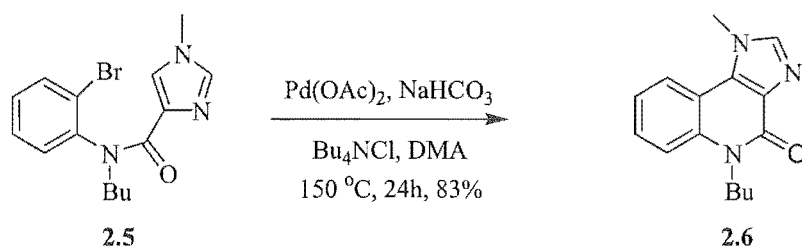
Scheme 2.3: Intramolecular Heck reaction for the synthesis of **2.2**.

Another brilliant example of the intramolecular Heck reaction is the cyclization of a pentacyclic lactam **2.3** with a pendant vinyl iodide moiety to give cyclic product **2.4**<sup>10</sup> (Scheme 2.4).



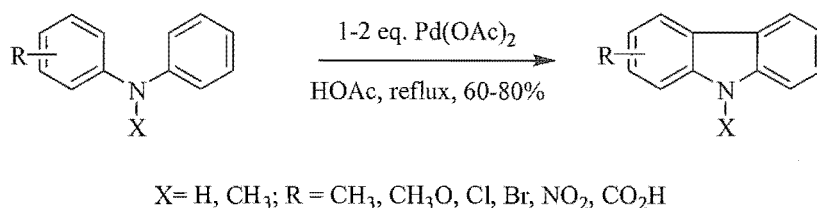
Scheme 2.4: Intramolecular Heck reaction of **2.3**.

An intramolecular heteroaryl Heck reaction was also the key step in the synthesis of 5-butyl-1-methyl-1*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one **2.6** which is a potent antiasthmatic drug<sup>11</sup> (Scheme 2.5).



Scheme 2.5: Intramolecular Heck cyclization for the synthesis of **2.6**.

In addition, the Mori-Ban indole synthesis involves the oxidative addition/cyclization process and stoichiometric carbopalladation using a Pd(II) species as well, typically from Pd(OAc)<sub>2</sub> (Scheme 2.6).<sup>12</sup>



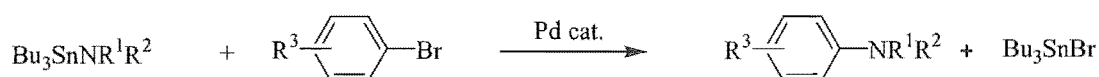
Scheme 2.6: Synthesis of indoles by Mori-Ban methodology.

The scope of this protocol is limited in most cases due to the consumption of a stoichiometric equivalents of expensive Pd(OAc)<sub>2</sub>. However, progress has been made towards a catalytic version of the Mori-Ban synthesis by Knölker's group in their synthesis of indoles.<sup>13</sup> Here, cupric acetate is used as a reoxidant of Pd(0) to Pd(II), as in Wacker's reaction.

In summary, Pd-catalyzed C-C bond formation has numerous applications in science. Compared to the considerable amount of research on C-C bond formation, little attention has been paid to the palladium-catalyzed direct C-N bond formation. What follows is an overview of Pd-catalyzed C-N bond synthesis.

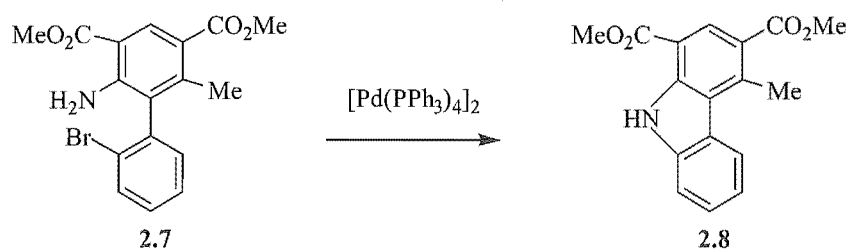
## 2.3 Overview of Pd-Catalyzed C-N Bond Formation

The first example of a Pd-catalyzed C-N bond formation was provided by Kosugi *et al.*<sup>14</sup> in 1983. They reported Pd-catalyzed transamination of aryl halides with aminostannanes leading to C-N bond formation (Scheme 2.7).



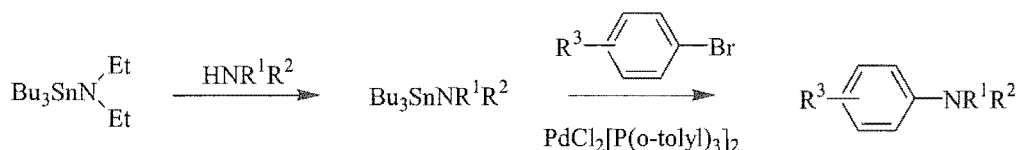
Scheme 2.7: Pd-catalyzed transamination of aryl halides with tin amides.

Unfortunately, the toxicity, thermal and moisture sensitivity, and the commercial non-availability of the aminostannanes limits the scope of this reaction. Moreover, its use is also limited to dialkyl aminostannanes and electron neutral aryl halides. In 1984, a Pd-mediated reaction involving a C-N bond synthesis was carried out by Boger *et al.*<sup>15</sup> via intramolecular amination of an aryl halide in the cyclization of the ring skeleton of lavendamycin **2.8** (Scheme 2.8).



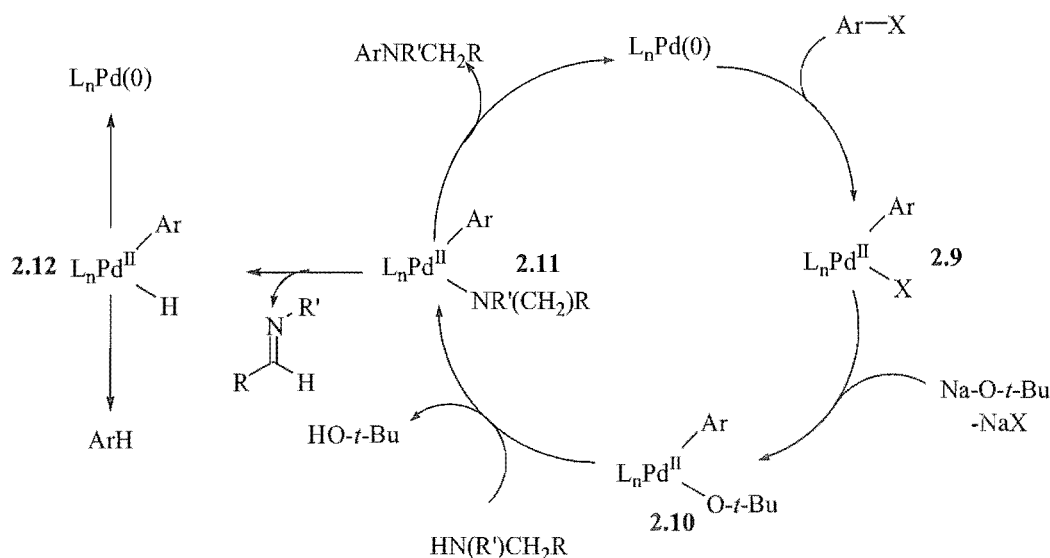
Scheme 2.8: Synthesis of **2.8** via Pd-catalyzed intramolecular amination of **2.7**.

Guram and Buchwald<sup>16</sup> then extended the ability of *N,N*-diethylaminostannanes to undergo transamination reactions by generating tin amides *in situ* as outlined in Scheme 2.9. The reactions proceeded with 80% yield or greater was still not practical because stoichiometric amounts of tin were required.



Scheme 2.9: Pd-catalyzed transamination of aryl halides by generating *in situ* tin amides.

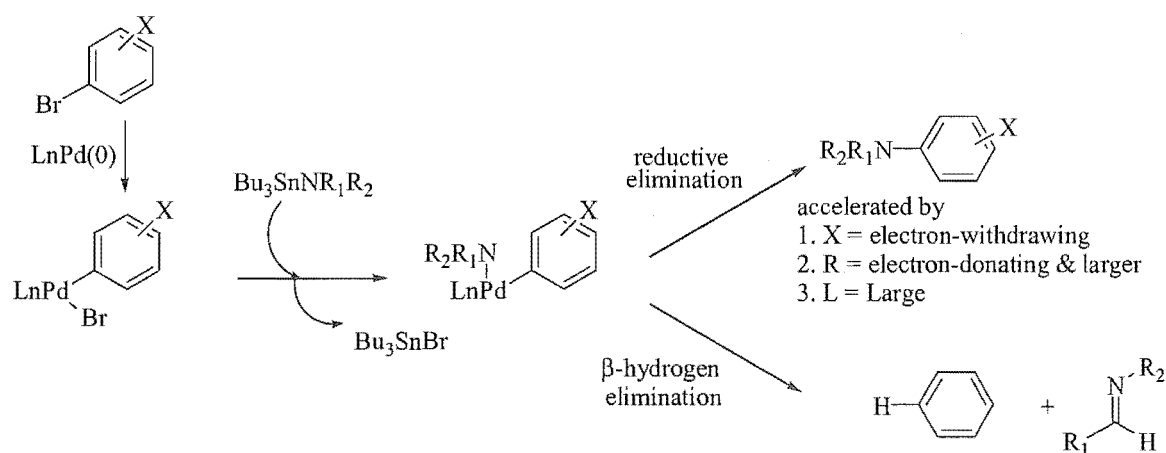
Amination under tin-free conditions was finally achieved independently by both Buchwald<sup>17</sup> and Hartwig groups<sup>18</sup> in 1995. These amination reactions were carried out by the reaction of an aryl halide with combination of an amine and an alkoxide, or a silylamide base, thus avoiding the isolation or generation of a tin amide *in situ*. The general reaction conditions are: bulky tris *o*-tolyl phosphine as ligand, a palladium catalyst, and 100 °C in toluene. Both groups report amination reactions using the above-mentioned conditions with a variety of substrates. A catalytic cycle for this process which is supported by mechanistic studies,<sup>19</sup> is illustrated in Scheme 2.10.



Scheme 2.10: Catalytic cycle of the amination of aryl halides.

Oxidative addition of palladium(0) to aryl halide results in the formation of complex **2.9**, which then reacts with an alkoxide or a silyl amide base to form an intermediate palladium alkoxide species **2.10**. This alkoxide species then undergoes ligand exchange with an amine to form the active amidopalladium complex **2.11** that undergoes reductive elimination of the amine.

A side reaction involved in catalytic cycle depicted in Scheme 2.10, is the  $\beta$ -hydrogen elimination reaction from the aryl amidopalladium complex **2.11** to give the arylpalladium(II) complex **2.12**, that undergoes reductive elimination to give an imine, a reduced arene, and Pd(0). Hartwig *et al.*<sup>21</sup> studied the effect of steric and electronic properties of ligands and halides on the relative rates of  $\beta$ -hydrogen elimination and reductive elimination of amine as summarized in Scheme 2.11.

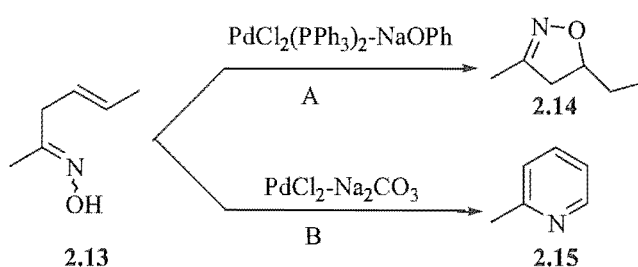


Scheme 2.11: Factors controlling the selectivity for amination vs  $\beta$ -H elimination.

This field has also gained significant interest over the past decade, and has been reviewed by many research groups.<sup>22</sup> What follows is a discussion on the Pd-mediated C-N bond synthesis from oximes, including introduction of the A-H reaction.

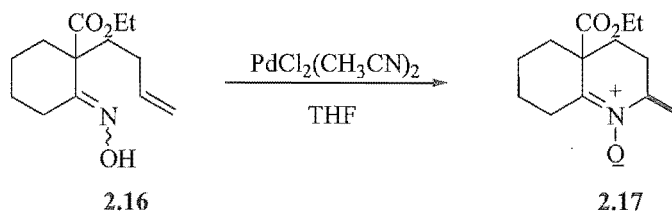
## 2.4 C-N Bond Formation via Pd-Mediated Cyclization of Oximes: The Advent of Amino-Heck Reaction

Oximes and their derivatives are widely used in organic synthesis as key intermediates in the preparation of a variety of heterocycles.<sup>23</sup> Murahashi *et al.* reported the transformation of  $\alpha,\beta$ -unsaturated ketoxime **2.13** into isoxazole **2.14** on treatment with an equimolar amount of  $\text{PdCl}_2(\text{PPh}_3)_2$  in the presence of 5 equivalents of NaOPh in benzene.<sup>24a</sup> Later on, they also reported the formation of pyridine derivative **2.15** in very low yields from **2.13** by Pd-catalyzed reactions<sup>24b</sup> (Scheme 2.12).



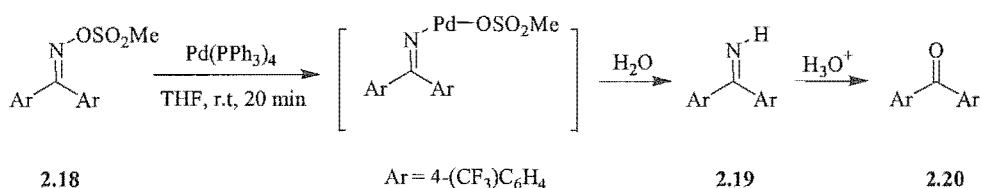
Schem 2.12: Synthesis of pyridines and isoxazoles from ketoximes.

Frederickson *et al.* also used palladium(II) salts in a oxime-nitrone-isoxazolidine cascade.<sup>25</sup> They reported the formation of cyclic nitrone **2.17** from  $\delta,\epsilon$ -unsaturated oxime **2.16** (Scheme 2.13). Here, the oxime directly attacks the olefinic moiety which is activated by coordination to palladium(II) complexes.



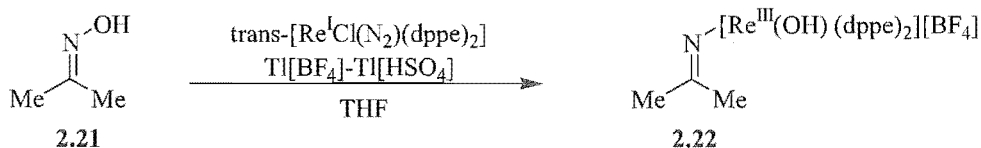
Scheme 2.13: Synthesis of cyclic nitrones from  $\delta,\epsilon$  unsaturated oximes.

Narasaka *et al.* recently reported the so-called Amino-Heck reaction, which is an intramolecular palladium-catalyzed cyclization (similar to Mizoroki-Heck reaction) of the olefinic derivatives of oximes, resulting in the synthesis of N-heterocycles.<sup>26</sup> They suggested the formation of an alkylideneaminopalladium(II) intermediate, similar to the  $sp^2$ -carbopalladium species in an intramolecular Heck reaction. Tsutsui *et al.* carried out the reaction of an equimolar amount of 4,4'-bis(trifluoromethyl) benzophenone *O*-methyl sulfonyl oxime **2.18** and  $Pd(PPh_3)_4$  in THF at room temperature to unravel the mechanism involved in such reactions<sup>26a</sup> (Scheme 2.14).



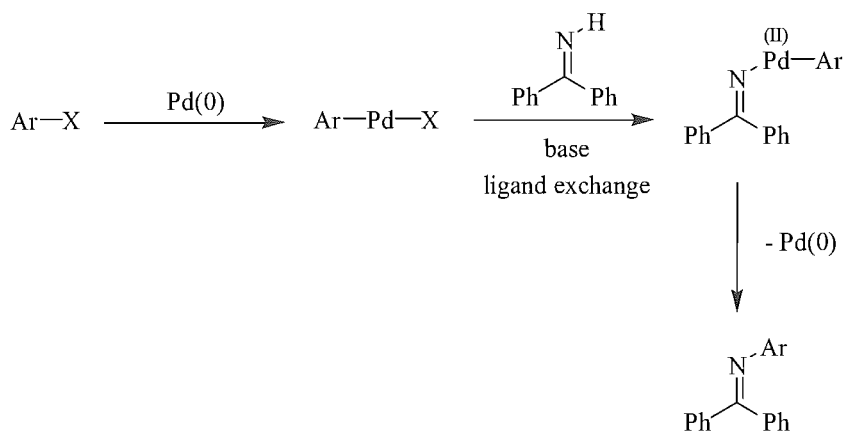
Scheme 2.14: Synthesis of **2.20** by the oxidative addition of Pd to the N-O bond of the oxime **2.18**.

A 4,4'-bis(trifluoromethylphenyl)methylideneamine **2.19** was isolated after quenching the reaction with a pH 9 buffer, and this was hydrolyzed to benzophenone **2.20** on treatment with an acid. Imine formation indicates that oxidative addition of Pd(0) to the N-O bond of oxime occurs, giving the intermediate diarylmethylideneaminopalladium(II) species that hydrolyzes to benzophenone via imine **2.19**. The formation of such an intermediate could not be observed directly in the above reaction, but Pombeiro *et al.*<sup>27</sup> have reported the isolation of a similar intermediate in the oxidative addition of an acetone oxime **2.21** to a rhenium(I) complex **2.22** (Scheme 2.15).



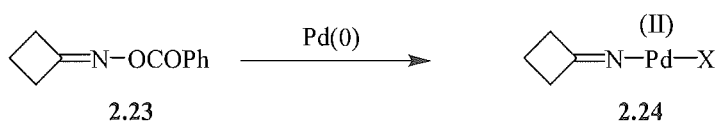
Scheme 2.15: Oxidative addition of Re(I) to the N-O bond of acetone oxime **2.21**.

Buchwald<sup>28a</sup> and Hartwig's<sup>28b</sup> groups have also reported previously the isolation of an alkylideneaminopalladium(II) species generated from arylpalladium(II) halides and diphenylmethyldeneamine via ligand exchange processes (Scheme 2.16).



Scheme 2.16: Synthesis of aryl imine via diphenylmethyldene Pd(II) intermediate.

The formation of an alkylideneaminopalladium(II) intermediate has also been suggested by Uemura *et al.* in their ring-opening reactions of cyclobutanone oximes<sup>29</sup> as shown in Scheme 2.17.

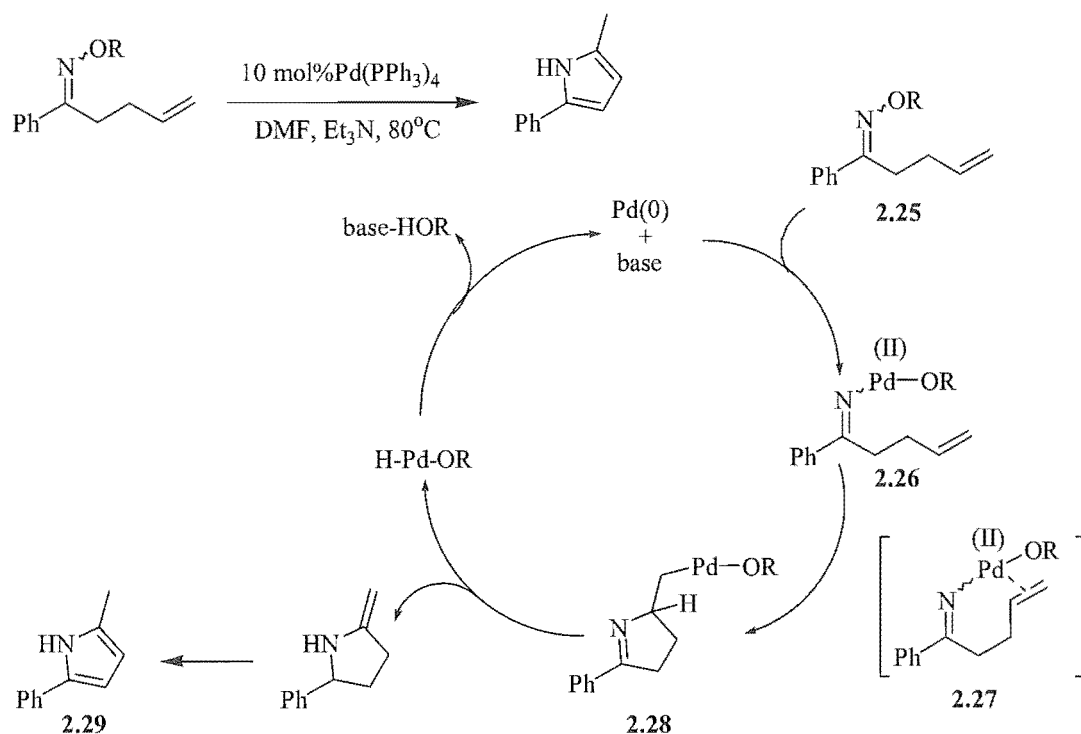


Scheme 2.17: Alkylideneaminopalladium(II) intermediate in the ring-opening reaction of 2.23.

Tsutsui *et al.*<sup>30</sup> synthesised various derivatives of pyrroles by carrying out an intramolecular amino Heck reaction of  $\gamma,\delta$ -unsaturated *O*-pentafluorobenzoyloximes. The suggested catalytic cycle for this A-H cyclization is depicted in Scheme 2.18. Oxidative addition of the N-O bond of oxime 2.25 to palladium(0) occurs to afford the alkylideneamino-palladium(II) intermediate 2.26. Olefin insertion into this species leads to the intermediate



**2.28** via **2.27**.  $\beta$ -hydrogen elimination from **2.28** gives rise to palladium hydride and the dihydropyrrole which isomerises to the final product pyrrole **2.29** in good yield.



Scheme 2.18: Palladium catalyzed synthesis of pyrroles from oximes.

The palladium hydride species then releases Pd(0) by reductive elimination to complete the catalytic cycle. The reaction is unaffected by the stereochemistry of oximes and work well with both *E* and *Z* oximes.<sup>26a</sup> What follows is a literature review revealing the significance of the A-H reaction in the synthesis of N-heterocycles.

## 2.5 Applications of A-H reactions to the synthesis of N-Heterocycles

The A-H reaction has successfully been used for the synthesis of functionalized pyrroles from various *O*-pentafluorobenzoyloximes as summarized in Table 2.1.<sup>30</sup>

Table 2.1: Synthesis of pyrroles by A-H cyclization of *O*-pentafluorobenzoyloximes.

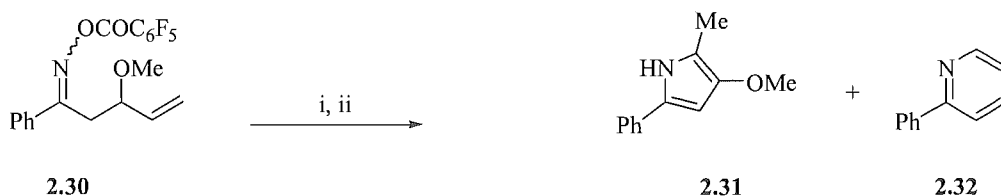
Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	% Yield
1	CH <sub>2</sub> CH <sub>2</sub> Ph	H	H	H	75 <sup>a</sup>
2	Ph	H	Me	H	80 <sup>b</sup>
3	CO <sub>2</sub> Et	H	H	H	45 <sup>b</sup>
4	Ph	H	H	Me	65 <sup>c</sup>
5	CO <sub>2</sub> Me	H	H	CO <sub>2</sub> Et	78 <sup>b</sup>
6	Ph	H	H	CO <sub>2</sub> Et	88 <sup>b</sup>

Reagents and Conditions: i) 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, Et<sub>3</sub>N, DMF, 80 °C. ii) isomerisation by  
 a) A-H reaction conditions. b) Me<sub>3</sub>SiCl, DCM. c) SiO<sub>2</sub>, DCM.

Several *O*-substituted oximes were examined, and only *O*-pentafluorobenzoyl derivatives were found to give the best result as it is thought to suppress the competing Beckmann rearrangement of oximes.<sup>30</sup> The reaction works well from both aliphatic and aromatic oxime substrates, containing electron rich and/or electron deficient olefins as depicted in Table 2.1.

The A-H reaction has also successfully been applied to the synthesis of pyrroles and pyridines from  $\gamma,\delta$ -unsaturated *O*-pentafluorobenzoyl oxime **2.30**.<sup>31</sup> Pyrrole **2.31** was obtained as the major product when the reaction was carried out under the optimum conditions of A-H reaction, and treatment of the crude reaction mixture with pyrrolidine

(Scheme 2.19). However, carrying out the reaction in the presence of 5 eq.  $(n\text{-Bu})_4\text{NCl}$  as an additive, and further treatment of the crude reaction mixture with pyrrolidine gave pyridine **2.32** as the major product as shown in Scheme 2.19.



Reagents and conditions:

i) a) 10 mol% $\text{Pd}(\text{PPh}_3)_4$ , DMF, 80 °C, TEA, 1h. b) pyrrolidine	69%	7%
ii) a) 10 mol% $\text{Pd}(\text{PPh}_3)_4$ , DMF, 80 °C, $(n\text{-Bu})_4\text{NCl}$ , TEA, 3h. b) pyrrolidine	11%	58%

Scheme 2.19: Synthesis of pyrrole **2.31** and pyridine **2.32** from ketooxime **2.30** using either conditions i or ii.

Various pyridine derivatives have been synthesized using the above reaction conditions (Figure 2.1).

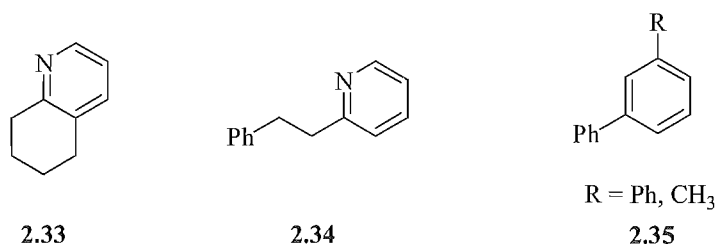
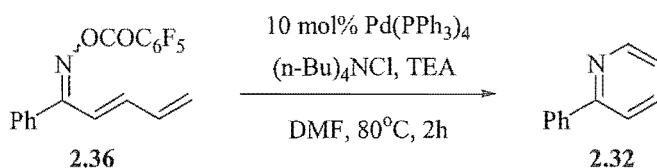


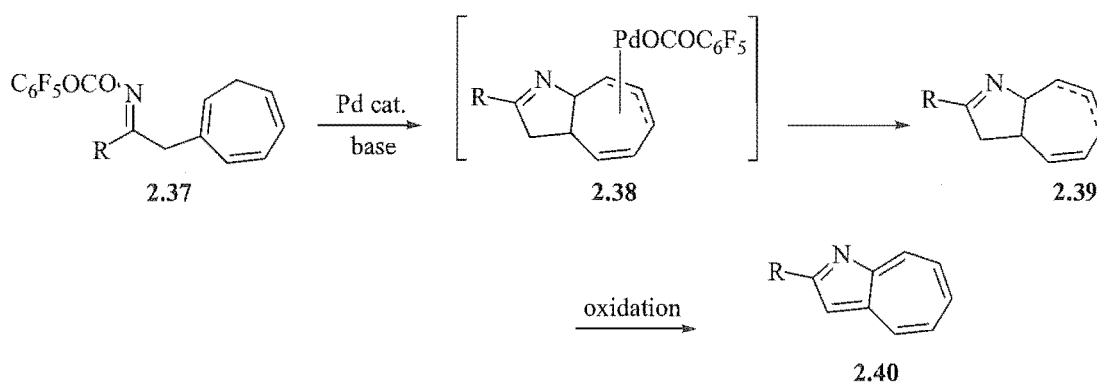
Figure 2.1: Pyridines formed by A-H reactions.

The reaction also works effectively with conjugated oxime substrate **2.36**, to give pyridine **2.32** in good yield<sup>31</sup> (Scheme 2.20).



Scheme 2.20: Synthesis of pyridine **2.32** from conjugated dienyl ketoxime **2.36**.

The same methodology has also been applied to the synthesis of a variety of 1-azaazulenes.<sup>32</sup> It is suggested that the A-H reaction of cycloheptatrienylmethyl ketone oxime **2.37** gives 3,4-dihydro-1-azaazulene **2.39** via the cyclic  $\pi$ -allyl-Pd intermediate **2.38**, which is transformed to 1-azaazulene **2.40** with successive  $\text{MnO}_2$  oxidation (Scheme 2.21).



Scheme 2.21: Synthesis of 1-azaazulenes via A-H/oxidation sequence.

Various 1-azaazulenes have been synthesized via A-H/oxidation sequence, and are summarized in Table 2.2 below.

Table 2.2 Synthesis of 1-azaazulenes by A-H cyclization/oxidation of *O*-pentafluorobenzoyloximes.

Entry	R <sup>1</sup>	R <sup>2</sup>	Time/h	% Yield
1	Ph	H	0.5	78
2	<i>t</i> -Bu	H	0.5	84
4		H	1.5	63
6	Ph	Me	0.5	52
7	Ph	Ph	0.5	55
9		H	1	68

Reagents and Conditions: i) 10 mol% Pd(dba)<sub>2</sub>, 40 mol% (*t*-Bu)<sub>3</sub>P, TEA, Ms 4Å, DMF, 80-100 °C, 0.5-1 h. ii) MnO<sub>2</sub>, DCM, reflux, 2h.

In summary, the A-H reaction has proved to be a very useful reaction in the synthesis of N-heterocycles from simple oxime substrates. The reaction works effectively under mild conditions, in polar solvents, and in the presence of both electron rich and electron deficient olefins. The reaction also works in a domino manner in conjunction with other chemical reactions, as exemplified by the synthesis of 1-azaazulenes.

The next three chapters cover further applications of A-H reaction to N-heterocycles' synthesis, investigated during the course of this research work.

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## **CHAPTER THREE**

### **SYNTHESIS OF SPIROCYCLIC IMINES BY DOMINO AMINO-HECK REACTION**

### 3.1 Introduction

The biological activity and other unique characteristics of N-heterocycles have made them attractive targets for medicinal and organic chemists. In recent decades, transition metal-catalyzed routes to N-heterocycles have become increasingly important. Here, the synthesis of spirocyclic imines using the domino A-H reaction is presented.

1-Azaspiro[4.4]nonane has a unique structure<sup>1</sup> and makes up the core skeleton of cephalotaxine **3.1**. This class of compounds has been of significant interest to organic chemists due to the powerful activity of its ester derivatives, harringtonine **3.2a** and homoharringtonine **3.2b**, against chronic myelogenous leukaemia (Figure 3.1). Homoharringtonine has also been investigated in the treatment of chloroquine resistant malaria.<sup>2</sup> Homoharringtonine is now in phase III clinical trials.<sup>3</sup> However, the natural sources of this alkaloid are very limited, and the plants from which it is extracted are endangered.<sup>4</sup>

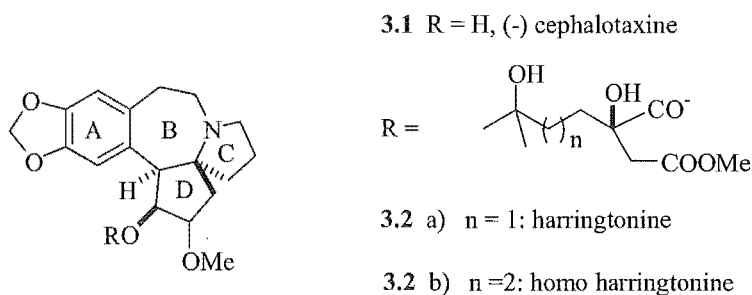
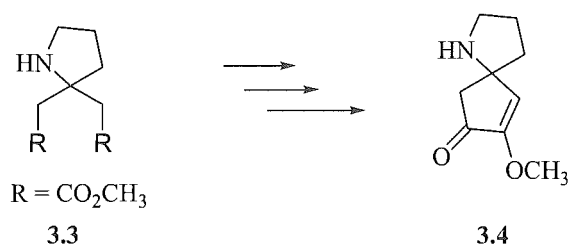


Figure 3.1: Cephalotaxus alkaloids.

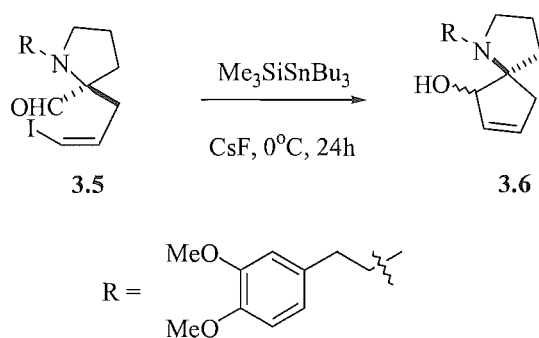
During the past three decades, many research groups have been involved in the total synthesis of cephalotaxine and its derivatives. The main synthetic problem, is the construction of the spiro quaternary centre at rings C and D, i.e. the 1-azaspiro[4.4]nonane skeleton. Therefore, various synthetic techniques have been developed towards the

synthesis of this moiety.<sup>5</sup> For example, Semmelhack *et al.*<sup>6</sup> reported the acyloin condensation of 1,1-bis(methoxycarbonylmethyl)pyrrolidine **3.3** to the resulting **3.4** (Scheme 3.1).



Scheme 3.1: Synthesis of **3.4** by acyloin type condensation.

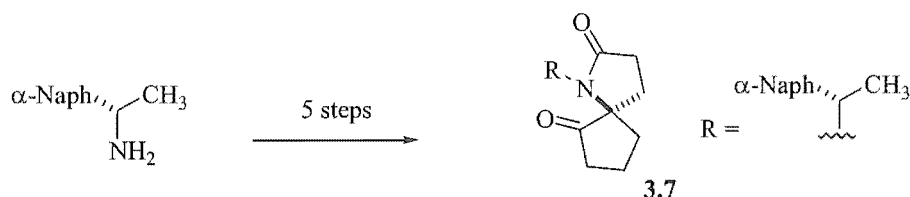
Mori *et al.*<sup>7</sup> have also reported the synthesis of the 1-azaspiro[4.4]nonane moiety **3.6** from (2*S*)-2-((*Z*)-3-Iodo-2-propenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]pyrrolidine-2-carbaldehyde **3.5** using stannyl anion generated from  $\text{Me}_3\text{SiSnBu}_3$  and CsF.



Scheme 3.2: Synthesis of **3.6** from **3.5**.

In 1999, Ikeda *et al.* published a synthesis from unnatural D-proline,<sup>8</sup> while Tietze performed an elegant and very efficient asymmetric synthesis based on palladium chemistry.<sup>9</sup>

Recently, Planas *et al.* synthesized an analogue of the same skeleton **3.7** starting from *S*-(1-naphthyl)-ethylamine in 5 steps in a stereoselective fashion.<sup>10</sup>

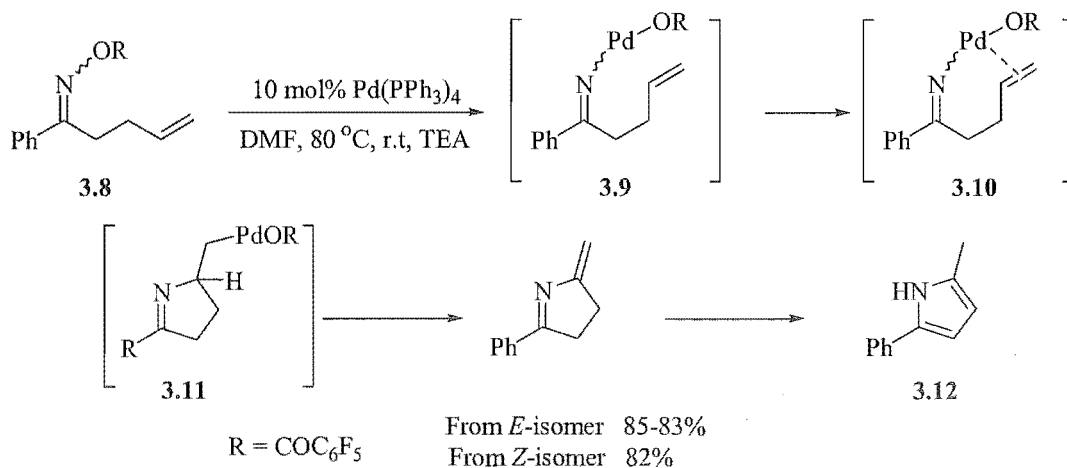


Scheme 3.3: Synthesis of **3.7**.

Herein, a simple and convenient route to the synthesis of 1-azaspiro[4.4]nonane analogues, using palladium-catalyzed domino A-H reactions is described.<sup>11a,11b</sup>

### 3.2 Synthetic Plan for the Domino A-H reaction

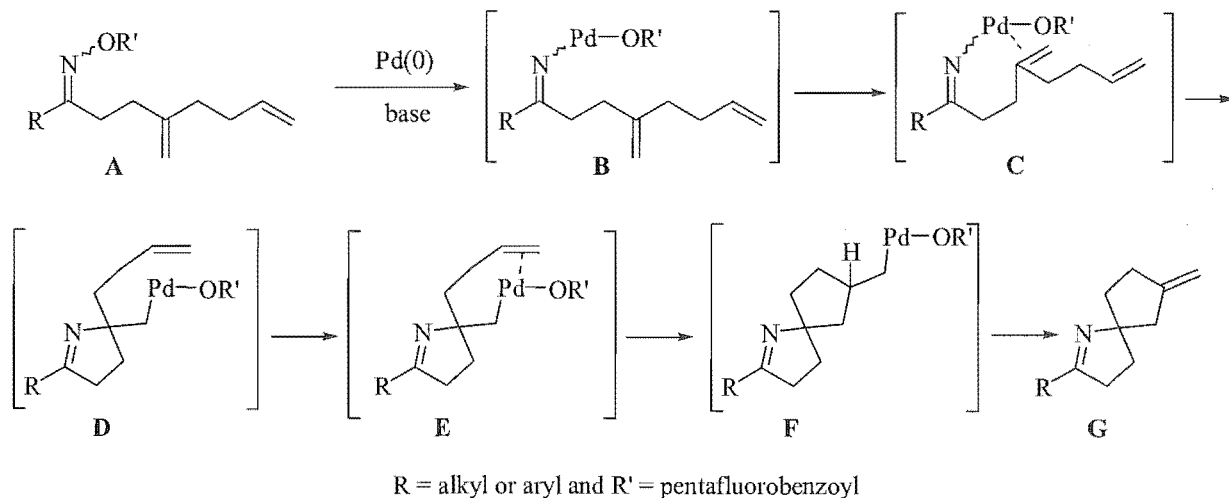
Narasaka *et al.* have recently introduced the A-H reaction which involves oxidative addition of the N-O bond of oximes to Pd(0) catalysts to generate an alkylideneaminopalladium(II) species, which can be used as intermediates in the synthesis of pyrroles from  $\gamma,\delta$ -unsaturated ketone oxime derivatives<sup>12</sup> (Scheme 3.4).



Scheme 3.4: Synthesis of pyrroles via Pd-catalyzed A-H reaction.

Thus,  $\gamma,\delta$ -unsaturated ketone oxime **3.8** reacts with  $\text{Pd}(\text{PPh}_3)_4$  to generate the alkylideneaminopalladium(II) species **3.9**, which then undergoes olefin insertion via intermediate **3.10** to give a palladium(II) intermediate **3.11**.  $\beta$ -Hydrogen elimination results in the formation of dihydropyrrole that isomerises to pyrrole **3.12**. The reaction is not affected by the stereochemistry of oxime and works well from both *E* and *Z* isomers.

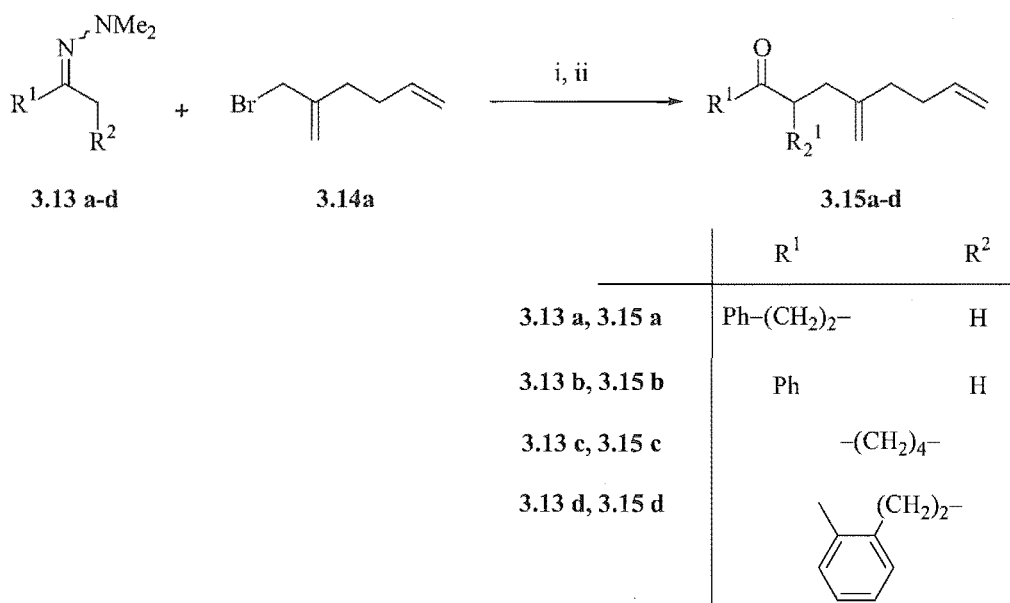
The outline of our synthetic strategy for the preparation of spiroimines is based on the domino cyclization initiated by the generation of alkylideneaminopalladium(II) species **B** from *O*-pentafluorobenzoyloxime **A** having a dienyl moiety. Thus, if an intermediate similar to **3.10** is lacking an appropriate  $\beta$ -hydrogen (e.g. intermediate **C**), then the complex may be long lived and susceptible to further cyclization in a domino<sup>13</sup> mode to give another intermediate **D**. The second alkene insertion into **D** will then give intermediate **F**,  $\beta$ -hydrogen elimination from which affords the spiroimine **E** as illustrated in Scheme 3.5.



Scheme 3.5: Synthetic plan for the synthesis of spiroimines by a domino A-H reaction.

### 3.3 Synthesis of the dienyl ketoximes for use in the Domino A-H reaction

The dienyl ketones **3.15a-d** were prepared as shown in Scheme 3.6. Aryl or alkyl ketone derivatives were synthesized by alkylation of the *N,N*-dimethylhydrazones **3.13a-d** with 2-bromomethyl-1,5-hexadiene<sup>13b</sup> **3.14a** and successive hydrolysis.<sup>14</sup> The crude dienyl ketone derivatives were purified by flash column chromatography to give **3.15a** (55%), **3.15b** (62%), **3.15c** (63%), **3.15d** (50%) and **3.15g** (63%).

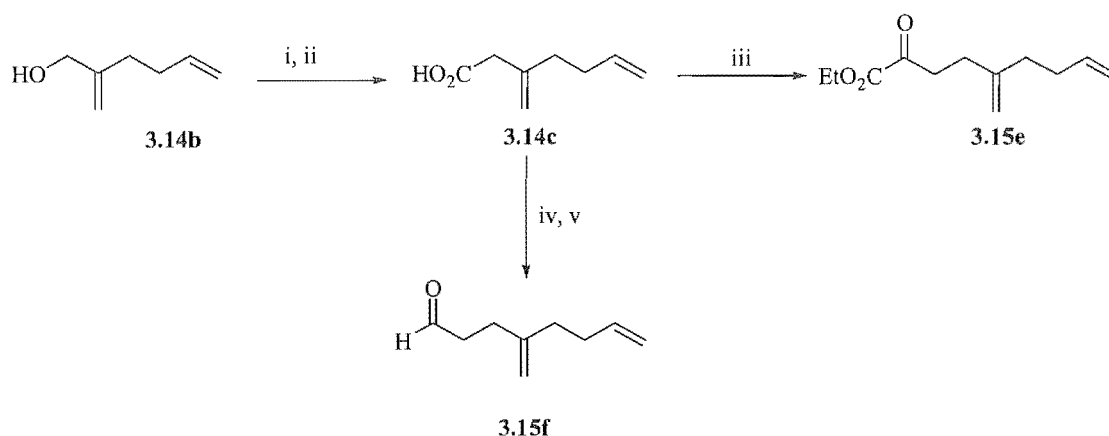


Reagents and conditions: i) LDA, THF, 1h; then 2-bromomethyl-1,5-hexadiene **3.14a**, -78°C-r.t, 16h.

ii) NaOAc, AcOH, THF, water, rt, 3h

Scheme 3.6: Synthesis of dienyl ketones **15a-d**.

$\alpha$ -Keto ester **3.15f** and aldehyde **3.15e**<sup>†</sup> were prepared from 2-methylene-5-hexen-1-ol<sup>13b</sup> (**3.14b**) as outlined in Scheme 3.7. Johnson-Claisen rearrangement of **3.14b**<sup>15</sup> and hydrolysis of the ester functionality afforded acid **3.14c**. The acid was then transformed to the desired  $\alpha$ -keto ester **3.15e** by using the methodology of Hangauer Jr.<sup>16</sup>



Reagents and conditions: i)  $\text{CH}_3\text{C}(\text{OEt})_3$ ,  $\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$ ,  $140^\circ\text{C}$ , 1.5 h. ii) aq.  $\text{NaOH}$ ,  $\text{MeOH}$ ,  $0^\circ\text{C}$ , 45 min. iii) 2LDA, TMEDA, THF, rt, 4h;  $(\text{EtOOC})_2$ ,  $-78$  to  $-40^\circ\text{C}$ , 1.5 h; aq.  $\text{NaHCO}_3$ . iv)  $\text{NHMe}(\text{OMe})\cdot\text{HCl}$ ,  $\text{Me}_2\text{N}(\text{CH}_2)_3\text{-N=C=N-CH}_2\text{CH}_3\cdot\text{HCl}$ , TEA, DCM, rt, 16h. v)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ,  $-40^\circ\text{C}$ , 20 min.

Scheme 3.7: Synthesis of aldehyde **3.15f** and  $\alpha$ -ketoester **3.15e**.

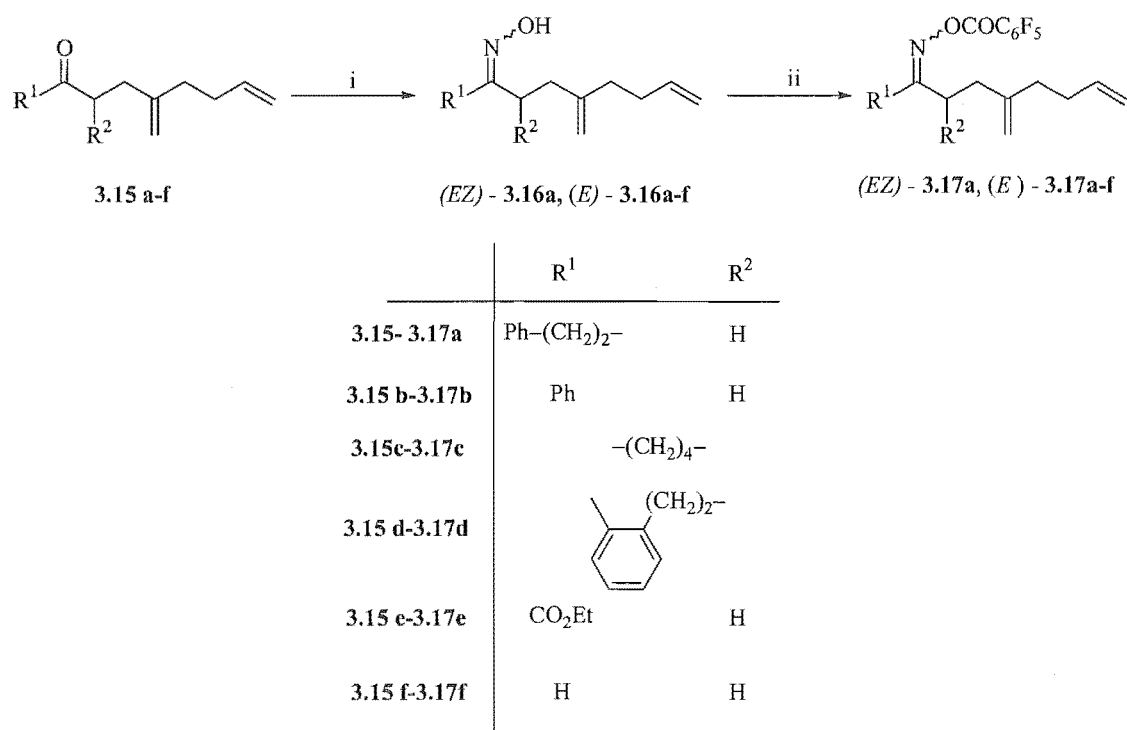
Aldehyde **3.15f**<sup>†</sup> was prepared from **3.14c** by transformation of the carboxyl group of the acid to a formyl group in two steps as shown in Scheme 3.7 above.

The dienyl ketones **3.15a-e** were treated with pyridine,  $\text{NH}_2\text{OH}\cdot\text{HCl}$  in  $\text{EtOH}$  at rt, stirred for 1-3 h and transformed to the corresponding oximes **3.16a-e**. The oximes were obtained as (*E*:*Z*) mixtures of **3.16a** (1:1, 97%), **3.16b** (8:1.5, 84%), **3.16c** (4:2, 90%), **3.16d** (single isomer, 80%) and **3.16g** (9:1, 95%) which were purified by flash column chromatography to elute the major isomers first and minor isomers later. The major isomers (or single isomer in case of **3.16d**) are tentatively assigned thermodynamically more stable *E* configuration. The *E*-isomers of oximes were observed to be comparatively less polar in all examples studied than the corresponding *Z*-oximes except **3.16a**, which was obtained as an inseparable mixture of isomers, and **3.16d** where a single isomer was formed.

<sup>†</sup> The synthesis and domino A-H reaction of  $\alpha$ -ketoester derivative **3.17e** and aldehyde derivative **3.17f** were carried out by a colleague, Dr. Mitsuru Kitamura at the University of Tokyo, Japan.

Isolation of the minor isomers (*Z*-**3.16b-c**, *Z*-**3.16g**) after column chromatography, and analysis by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy revealed a slow isomerisation at rt to the more stable *E*-isomers.

The oximes [(*EZ*)-**3.16a** (1:1), *E*-**3.16b-g**] were then treated with TEA,  $\text{C}_6\text{F}_5\text{COCl}$  at  $0\text{ }^\circ\text{C}$ , and stirred for 1-2 h to give *O*-pentafluorobenzoyl oximes [(*EZ*)-**3.17a** (1:1), *E*-**3.17b-g**]. Purification by flash column chromatography gave (*EZ*)-**3.17a** (1:1, 95%), (*E*)-**3.17b** (87%), (*E*)-**3.17c** (77%), (*E*)-**3.17d** (75%) and (*E*)-**3.17g** (80%). No isomerisation was observed for these oximes [(*EZ*)-**3.17a** (1:1), (*E*)-**3.17b-g**] in the pentafluorobenzoylation step and subsequent column chromatography. The *E/Z* ratios were determined by analysis of  $^1\text{H}$  NMR spectra of the corresponding oximes and *O*-pentafluorobenzoyl oximes.

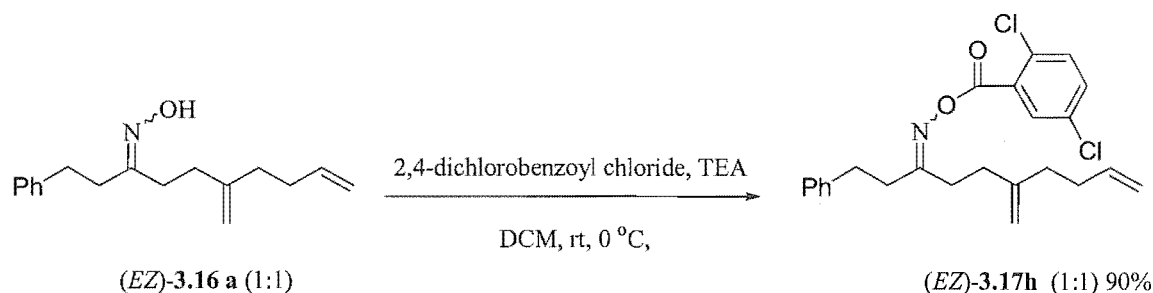


Reagents and conditions: i) Pyridine,  $\text{NH}_2\text{OH} \cdot \text{HCl}$ , EtOH, rt, 1-3 h. ii)  $\text{C}_6\text{F}_5\text{COCl}$ , TEA, DCM, rt,  $0\text{ }^\circ\text{C}$ , 1-2 h.

Scheme 3.8: Synthesis of oximes **3.16a-f** and *O*-pentafluorobenzoyl oximes **3.17a-f**.



In addition to *O*-pentafluorobenzoyl oximes (*EZ*)-3.17a, (*E*)-3.17b-g, *O*-2,4-dichlorobenzoyloxime derivative (*EZ*)-3.17h (1:1) of oxime *EZ*-3.16a was also synthesized to check the effect of a different *O*-substituted group on the domino A-H reaction (Scheme 3.9). *O*-benzoyl, *O*-diphenylphosphinoyl and *O*-trifluoroacetyl groups are reported unsuitable for A-H reaction as oximes bearing such groups react slowly and with Beckmann rearrangement.<sup>12</sup>



Scheme 3.9: Synthesis of *O*-2,4-dichlorobenzoyl oxime *EZ*-3.17h.

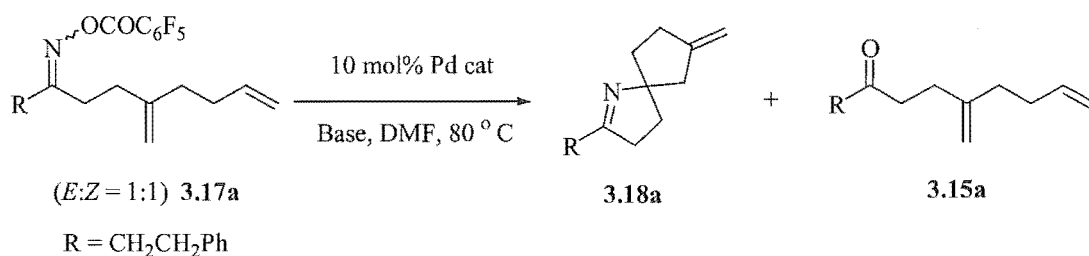
### 3.4 Optimization of reaction conditions for the Domino A-H reaction

An initial study was carried out on the spirocyclization of the dienyl oxime derivative (*EZ*)-3.17a as shown in Table 3.1. Using the optimal conditions of the previous pyrrole synthesis<sup>12</sup>, i.e. at 80 °C with 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> and TEA in DMF, required 11.5 h to consume (*E*)-3.17a. The desired spiroimine 3.18a was obtained in 60% yield accompanied by 34% of ketone 3.15a (entry 1). Although the use of Pd(dba)<sub>2</sub> and PPh<sub>3</sub> accelerated the reaction, the yield of cyclized product 3.18a was not improved, but a larger amount of the ketone 3.15a was obtained (entry 2).

To improve the yield of the cyclization product 3.18a, it was required to suppress the formation of ketone 3.15a. The ketone could be formed either by protonation of the initially formed alkylideneaminopalladium(II) complex **B** (Scheme 3.5) with the resulting

ammonium salt ( $\text{Et}_3\text{NH}^+ \cdot \text{C}_6\text{F}_5\text{COO}^-$ ) and/or contaminated water, or by the reductive elimination from palladium hydride species ( $\text{H-Pd-N}=\text{C}$ ) generated from **B** and TEA and successive  $\beta$ -hydrogen elimination.<sup>17</sup> To check the effect of amine having  $\beta$ -hydrogen, a base having no  $\beta$ -hydrogen like DABCO was used as a base for the cyclization. The yield of **3.18a**, however, was not improved and 53% of the ketone **3.15a** was formed instead (entry 3).

Table 3.1: The Domino A-H reaction of **3.17a**.



Entry	Pd cat	Base	Time/h	Yield <sup>a</sup> /%	
				<b>3.18a</b>	<b>3.15a</b>
1	$\text{Pd}(\text{PPh}_3)_4$	TEA	11.5	60	34
2	$\text{Pd}(\text{dba})_2 + n\text{PPh}_3^{\text{b}}$	TEA	1-8	17-53	78-42
3	$\text{Pd}(\text{PPh}_3)_4$	DABCO <sup>c</sup>	12	31	53

a) isolated yield. b)  $n = 2, 4$  or  $6$ . c) diazobicyclo[2.2.2]octane

Palladium(II) chlorides such as  $\text{PdCl}_2[\text{P}(o\text{-tol})_3]_2$ ,  $\text{PdCl}_2[\text{P}(c\text{-hex})_3]_2$ ,  $\text{PdCl}_2(\text{dppf})$ , and  $\text{PdCl}_2(\text{dppp})$  were not suitable for this cyclization, as the yields of the imine were very low i.e. 23%, 30%, 39% and 18% respectively. Therefore,  $\text{Pd}(\text{PPh}_3)_4$  was used in further optimization.

The reaction was accelerated at higher temperature (110 °C) and the yield of the spirocyclic imine **3.18a** was improved to 70% (Table 3.2, entry 1). Of the various bases examined

(entry 2-4), the best results were obtained with  $K_2CO_3$ , but poor reproducibility was observed (entry 4). Therefore, TEA was used as a base for further studies.

Cyclization proceeded smoothly in polar aprotic solvents (entries 5, 6) compared to non-polar solvents (entry 7). DMF was found to be more suitable than  $CH_3CN$  due to the low boiling point of  $CH_3CN$  (entry 8).

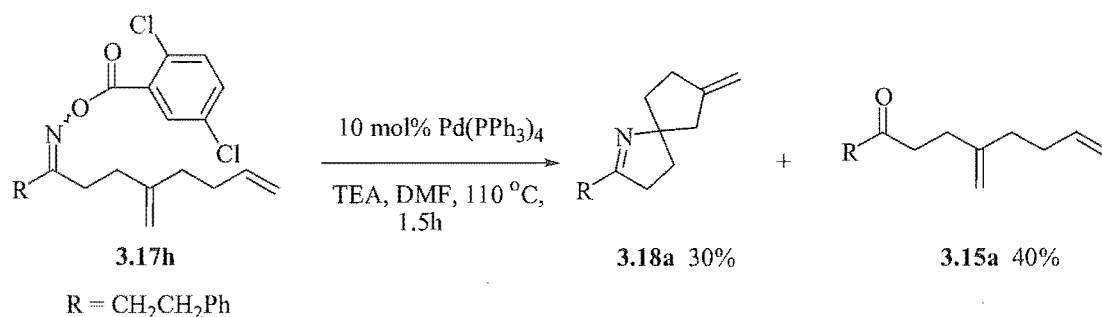
Table 3.2: Optimization of reaction conditions of the Domino A-H reaction of **3.17a** using  $Pd(PPh_3)_4$ .<sup>a)</sup>

Entry	Base (mol amount)	Temp/ $^{\circ}C$	Solvent	Time/h	Yield% <sup>b)</sup>	
					<b>3.18a</b>	<b>3.15a</b>
1	TEA (5.0)	110	DMF	0.5	70	22
2	<i>t</i> -BuOK (2.0)	110	DMF	0.5	22	33
3	$CS_2CO_3$ (2.0)	110	DMF	0.5	53	18
4	$K_2CO_3$ (2.0)	110	DMF	1	60-82	20-5
5	TEA (5.0)	110	DMF	0.5	70	22
6	TEA (5.0)	110	DMPU <sup>c)</sup>	0.5	53	18
7	TEA (5.0)	110	toluene	2	22	33
8	TEA (5.0)	110	$CH_3CN$	6.5	45	37

a) **3.17a**:  $Pd(PPh_3)_4$  = 1:0.1. b) Isolated yield. c) DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone.

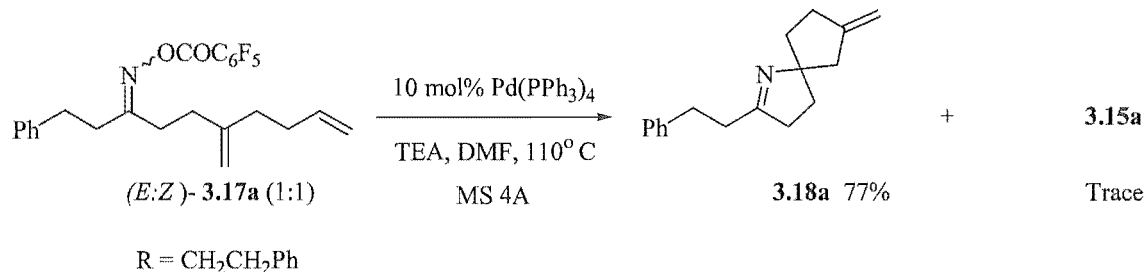
Next, the domino A-H reaction of (*E/Z* = 1:1)-**3.17h** was carried out to check the effect of a different *O*-substituted group on A-H reaction. Unfortunately, only 30% of the cyclic imine was formed, along with 40% of the side product ketone **3.15a** (Scheme 3.10). This result suggests that *O*-pentafluorobenzoyl group suppresses the competing Beckmann

rearrangement, as very little or no ketone is formed during the A-H reaction of the corresponding *O*-pentafluorobenzoyl derivatives of oximes.



Scheme 3.10: The Domino A-H reaction of **3.17h**.

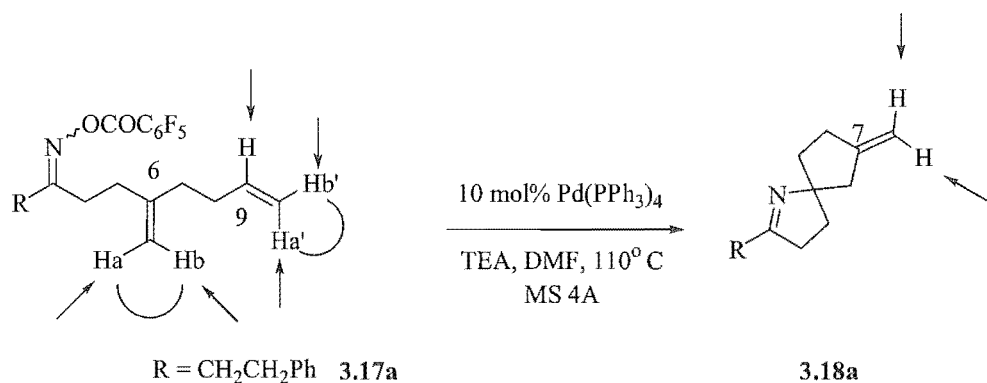
Finally, the use of molecular sieves 4 Å (MS 4 Å) in the reaction resulted in an improved yield of 77%, and the formation of ketone was suppressed to a trace amount



Scheme 3.11: The Domino A-H reaction of **3.17a** in the presence of MS 4A.

(Scheme 3.11). It would seem likely that the molecular sieves trap a trace amount of moisture or acidic protons that prevent the protonolysis of the aminopalladium species **B** (Scheme 3.5).

The product for the domino A-H reaction was clearly characterized from the  $^1\text{H}$  NMR spectrum by the absence of the olefinic protons at position 6, 9 and 10 of **3.17a** and the appearance of methylene protons at position 7 of **3.18a** (Figure 3.2).



X-H	$\delta$ ppm (multiplicity)	X-H	$\delta$ ppm (multiplicity)
6-Ha	4.66 (s), 4.68 (s)	7-CH <sub>2</sub>	4.87 (s)
6-Hb	4.70 (s), 4.71 (s)		
9-H	5.96-5.78 (m)		
10-Ha'	4.88 (dd)		
10-Hb'	4.96 (dd)		

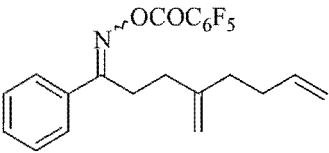
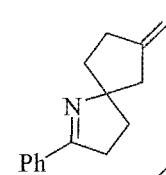
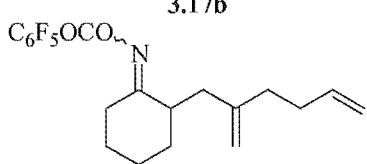
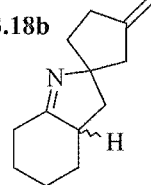
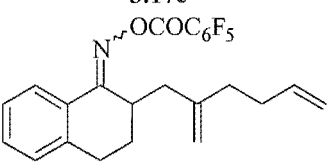
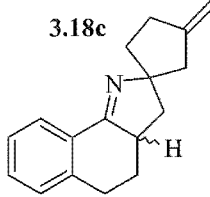
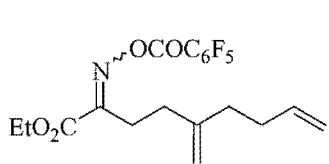
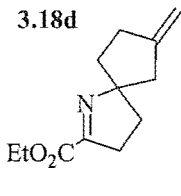
Figure 3.2: Comparison of  $^1\text{H}$  NMR resonances for **3.17a** and **3.18a**.

In addition, the  $^{13}\text{C}$  NMR spectral data and elemental analysis reports also confirmed the structure and mass of the product **3.18a**.

### 3.5 The Domino A-H reactions of *O*-pentafluorobenzoyl oximes

The scope of the palladium-catalyzed domino cyclization was extended as shown in Table 3.3 by using the optimum conditions from previous study described in section 3.4 i.e. 10 mol% of  $\text{Pd}(\text{PPh}_3)_4$  and 5 molar amounts of TEA as a base in DMF in the presence of MS 4Å at 110 °C.

Table 3.3: Synthesis of spirocyclic imines by the domino A-H cyclization of *O*-pentafluorobenzoyl oximes.<sup>a)</sup>

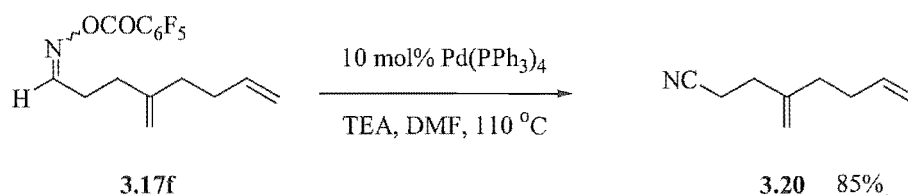
entry	oxime	product	Yield(%) <sup>b</sup>
1	 <b>3.17b</b>	 <b>3.18b</b>	(82)
2 <sup>c)</sup>	 <b>3.17c</b>	 <b>3.18c</b>	64 (1:1) <sup>d)</sup>
3	 <b>3.17d</b>	 <b>3.18d</b>	80 (1:1) <sup>d</sup>
4	 <b>3.17e</b>	 <b>3.18e</b>	(76)

a) Isolated yields, b) time=1h, c) determined by <sup>1</sup>H nmr d) time=20 min

Phenyl ketone oxime *E*-**3.17b** cyclized smoothly to **3.18b** in 82% yield (entry 1). Cyclohexanone oxime derivative *E*-**3.17c** cyclized and gave tricyclic imine **3.18c** as a 1:1 diastereoisomeric mixture (1:1, based on analysis of <sup>1</sup>H NMR spectrum) in moderate yield (entry 2). Similarly, the tetracyclic imine **3.18d** was obtained as a diastereoisomeric mixture (1:1, determined from <sup>1</sup>H NMR) in 80% yield by using a tetralone oxime derivative *E*-**3.17d** (entry 3). Cyclic imine having ethoxycarbonyl group **3.18e** was also synthesized

from the oxime derivative of  $\alpha$ -keto ester *E*-**3.17e** (entry 4). Thus, keto oximes were successfully converted to spiroimines.

In contrast to the ketoximes, the aldoxime *E*-**3.17f** did not cyclize and gave exclusively the corresponding nitrile **3.20** by Beckmann fragmentation<sup>18</sup> (Scheme 3.12).



Scheme 3.12: Beckmann fragmentation of **3.17f** under A-H reaction conditions.

The nitrile **3.20** is probably formed via generation of the alkylideneaminopalladium(II) intermediate and successive fragmentation,<sup>19</sup> as depicted in Figure 3.3.

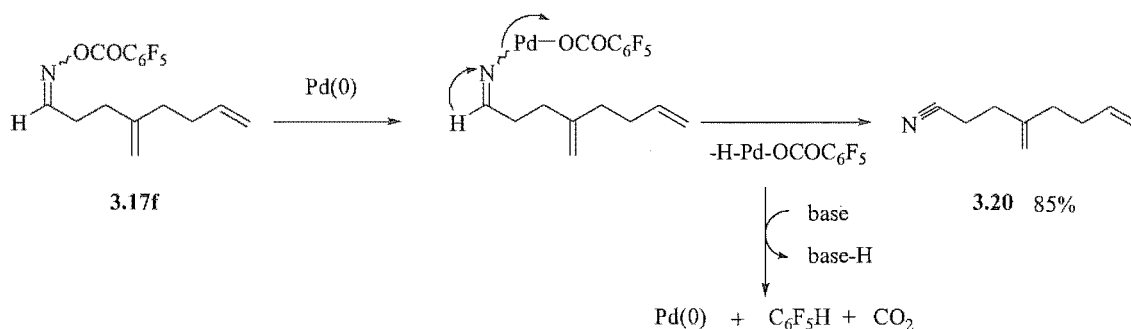
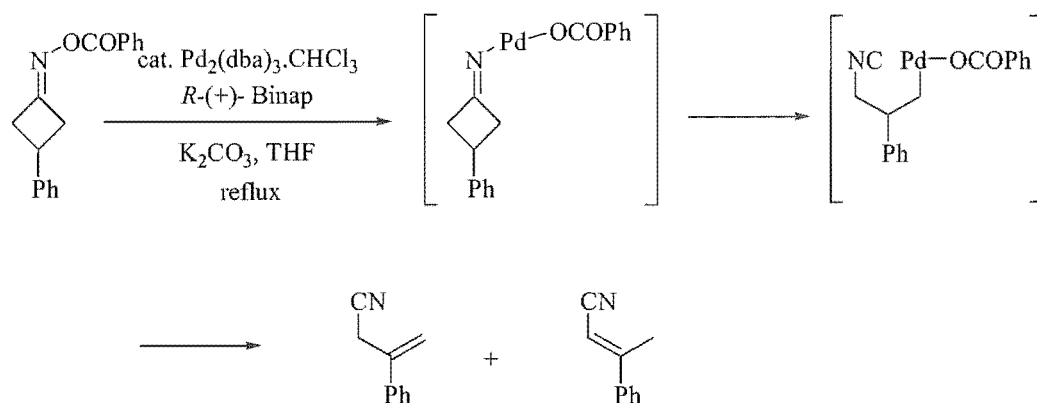
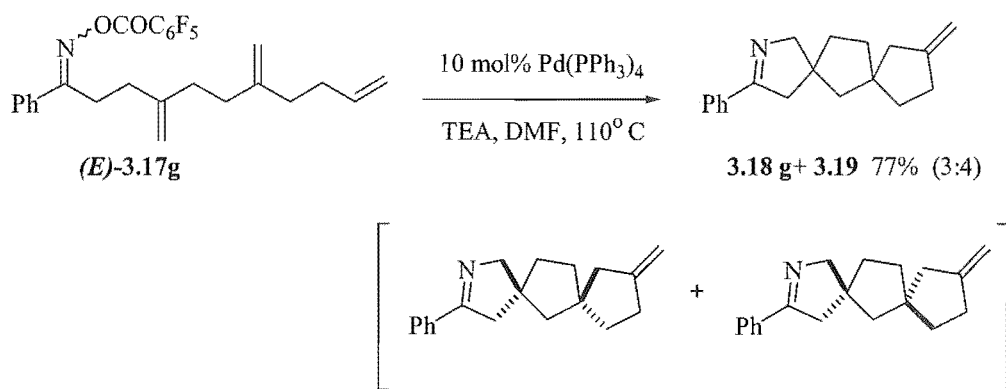


Figure 3.3: Plausible mechanism for the formation of nitrile **3.20**.

The nitrile formation from the alkylideneaminopalladium(II) intermediate is also supported by a recent report by Uemura *et al.*, who have reported a palladium-catalyzed nitrile synthesis<sup>20</sup> from cyclobutanone *O*-acyloximes (Figure 3.4).

Figure 3.4: nitrile formation from cyclobutanone *O*-acyloxime

Further extension of the domino A-H reaction of the dienyl oxime to a trienyl olefinic oxime **3.17g** resulted in the formation of a diastereomeric mixture (3:4, based on analysis of  $^1\text{H}$  NMR spectrum) of tricyclic imine **3.18g** and **3.19** as shown in Scheme 3.13.

Scheme 3.13: The Domino A-H reaction of **3.17g**.

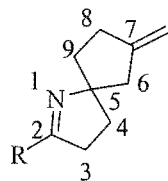
Preparative thin layer chromatography allowed for the separation of the diastereomeric mixture and the diastereomer with high  $R_f$  value was obtained as the major fraction in 44% yield and characterized while the second isomer was obtained in 33% yield and was also



characterized by  $^1\text{H}$ ,  $^{13}\text{C}$  NMR spectroscopy. The reaction afforded the tricyclic imine in a combined yield of 77%. (Configuration of the isomers was not assigned).

All spiroimines (**3.18a-g**, **3.19**) were characterized by  $^1\text{H}$ ,  $^{13}\text{C}$  NMR spectroscopy, and microanalysis or mass spectrometry. The characteristic  $^{13}\text{C}$  NMR chemical shifts for C-7 methylene protons-attached carbon, C-7, and spirocentre C-5 and C=N are summarized in Table 3.4.

Table 3.4: Characteristic  $^{13}\text{C}$  chemical shifts of the spiroimines.

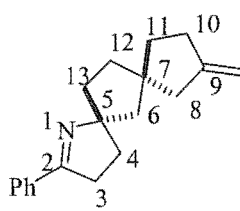
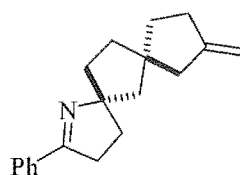


Compound #	2-C=N	C-5	C-7	$\text{CH}_2=\text{C-7}$
<b>3.18a</b>	175.2	82.1	150.9	106.1
<b>3.18b</b>	170.6	82.8	151.0	106.1
<b>3.18c</b>	177.1	80.5, 80.6	151.0	106.0, 106.1
<b>3.18d</b>	171.5	80.9, 80.9	151.0, 151.1	105.9, 106.1

Bicyclic spiroimines (**3.17a-d**) exhibited the chemical shifts for C-5 within the range of  $\pm 2.5$  ppm between 80.5 and 82.8 ppm, whereas C-7 resonated just with a difference of 0.2 ppm. Likewise, the C bearing the methylene protons also resonated with a minor difference of only 0.1 ppm. The chemical shifts for the imino carbons (C=N) for **3.18b** and **3.18d** were observed 5-7 ppm upfield compared to **3.18a** and **3.18c**. This could be attributed to charge delocalization by the phenyl group  $\alpha$ - to C=N in **3.18b** and **3.18d**, which make these carbon less electron deficient and hence an upfield chemical shift is observed.

The characteristic  $^{13}\text{C}$  NMR chemical shifts for the trispiranes (**3.18g**, **3.19**) are shown in Table 3.5. The chemical shifts for major isomer for  $\text{C}=\text{N}$ ,  $\text{C}-5$ ,  $\text{C}-9$  and  $\text{C}(9)=\text{CH}_2$  exhibits the same pattern of chemical shifts as for  $\text{C}=\text{N}$ ,  $\text{C}-5$ ,  $\text{C}-7$  and  $\text{C}(7)=\text{CH}_2$  for bicyclic spiranes (**3.17a-d**), but the minor isomer exhibits the chemical shifts for  $\text{C}-5$ ,  $\text{C}-7$  about 26ppm and 9.1 ppm downfield.

Table 3.5: Characteristic  $^{13}\text{C}$  chemical shifts of the spiroimines **3.18g** and **19**.

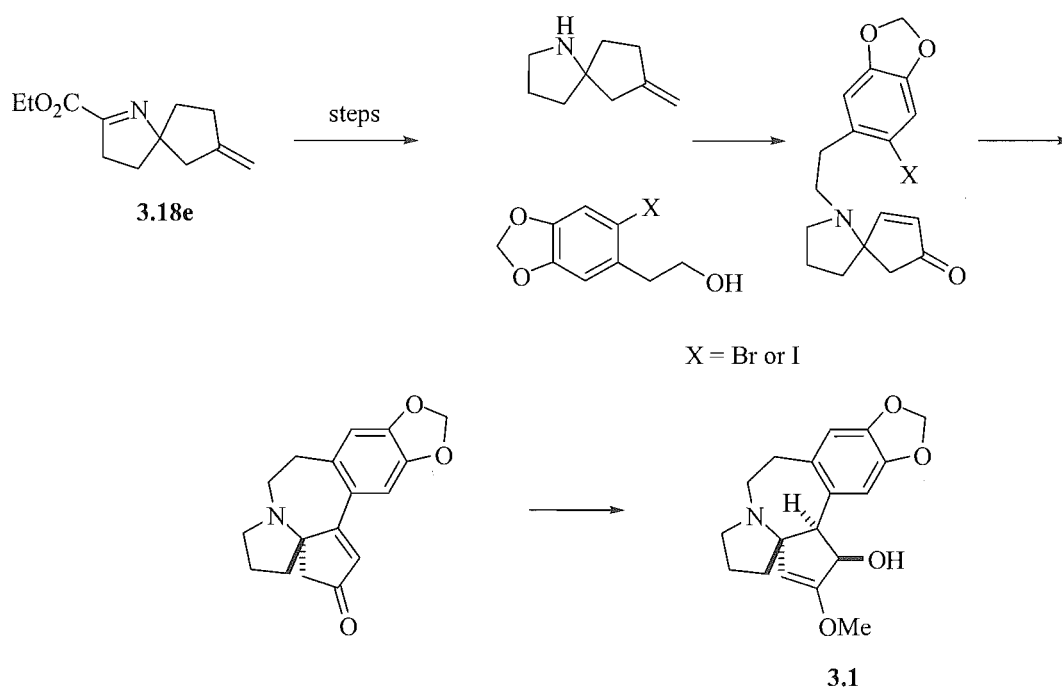



3.18g and 19					
Compound #	$\text{C}=\text{N}$	$\text{C}-5$	$\text{C}-7$	$\text{C}-9$	$9-\text{C}=\text{CH}_2$
major	169.5	83.3	50.0	105.4	152.8
minor	169.0	109.3	50.0	114.5	152.5

### 3.6 Conclusion and Future Work

In summary, the domino A-H reaction has proven to be a convenient and general method for the preparation of spiroimines from dienyl or trienyl ketone *O*-pentafluorobenzoyl oximes. The reaction proceeds by treatment with a catalytic amount of  $\text{Pd}(\text{PPh}_3)_4$ , TEA, and MS 4Å via the formation of alkylideneaminopalladium(II) intermediates generated *in situ* by the oxidative addition of oximinoesters to the  $\text{Pd}(0)$  complex. By increasing the olefinic moiety in the starting material, polycyclic imines can be easily constructed in one pot synthesis by the use of palladium-catalyzed domino A-H cyclizations.

Future work in this area could involve carrying out the domino A-H reaction in an asymmetric manner by treatment of (*R*) or (*S*) BINAP in combination with palladium catalysts. The ester derivative of the spirocyclic imine **3.18e** could also be used in a multistep synthesis to the total synthesis of cephalotaxine as depicted in Scheme 3.12.



Scheme 3.14: Proposed total synthesis of Cephalotaxine **3.1** from **3.18e**.

Additionally, by introducing different kinds of olefinic moieties into the substrates, the A-H reaction can also be extended to ene-yne type of domino cyclization.

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## **CHAPTER FOUR**

### **SYNTHESIS OF TRI-SUBSTITUTED IMIDAZOLES BY AMINO-HECK REACTION**

## 4.1 Introduction

There is an ongoing interest in the development of new methods for the synthesis and derivatization of heterocyclic compounds. Imidazoles, an important class of N-heterocycles, have numerous applications in organic synthesis, and are components of an array of biomolecules. Here, a further application of the A-H reaction to the synthesis of aliphatic and C-terminal amino acid-based imidazoles as a generalized method is presented. What follows is a brief review of some biologically active imidazoles and methods of their synthesis.

An imidazole is a component of the essential amino acid histidine and related compounds, and is well known as ligand in many metalloproteases.<sup>1</sup> The metal ion coordination in these complex molecules generally takes place via N(1) or N(3) of imidazole residues as exemplified by myoglobin and other heme proteins, carbonic anhydrase, and carboxy peptidase. Another example is thermolysin (TLN), a heat-stable proteolytic enzyme that contains two histidine residues coordinated to zinc ion.<sup>2a,b</sup> A crystal structure<sup>2c</sup> of the TLN is depicted in Figure 4.1: the active site of the enzyme shows a tetrahedral Zn ion bound to two histidine residues via N(1) in each case.



Figure 4.1: Crystal structure of the metalloprotease TLN highlighting the  $\alpha$  - helical structure of the active site (yellow) containing two histidines (green/blue) bound through their N(1) to tetrahedral  $\text{Zn}^{2+}$  (white).

The proposed reaction mechanism of peptide bond hydrolysis<sup>2a</sup> by TLN is illustrated in Figure 4.2.

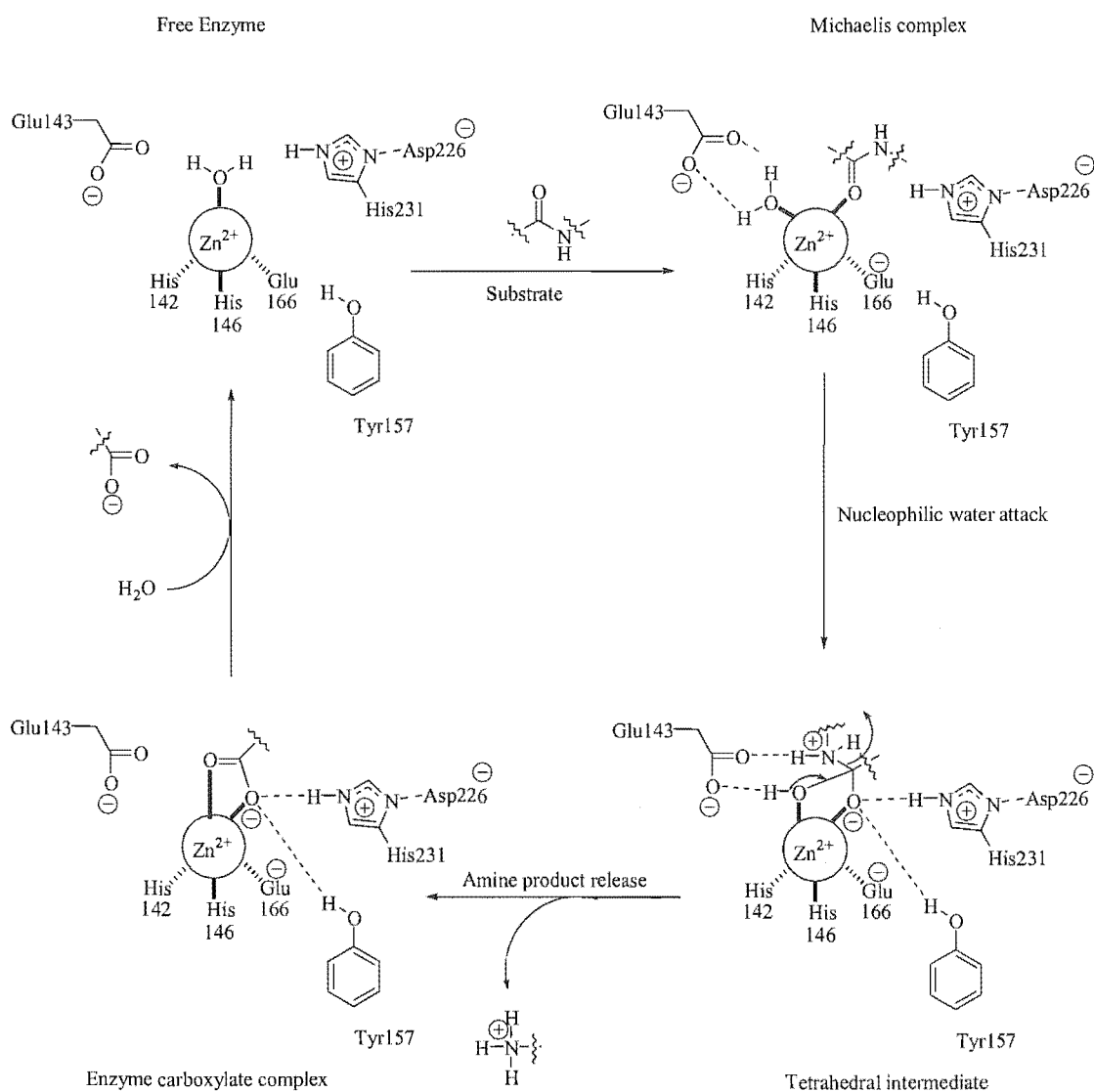


Figure 4.2: Experimentally proposed catalytic cycle for TLN.

Four amino acid residues Glu143, His231, Tyr157 and Asp226 take part in the catalytic pathway. The Zn<sup>2+</sup> ion is coordinated to a water molecule, His142, His146 and Glu166 in



the inactivated form of TLN. A wide groove exists between the two domains of the enzyme to accommodate the extended peptide chain of the substrate thus forming Michaelis complex. The carbonyl oxygen of the scissile peptide wedges between His231, Tyr157 and water molecule in the proximity of  $\text{Zn}^{2+}$ . The water molecule is then displaced towards Glu143 resulting in a strong polarization between the negative carboxylate and the  $\text{Zn}^{2+}$ . This increases the nucleophilicity of the water oxygen, to promote attack on the carbonyl carbon. The proton accepted by Glu143 is immediately shuttled to the nitrogen of the substrate to give a tetrahedral complex, where Zn is pentacoordinated and the peptide C is tetrahedral. The formation of hydrogen bonds to His231 and Tyr157 enhances the formation of this tetrahedral complex. The negative carboxylate motif of Asp226 helps to stabilize the positive charge required for catalysis. Direct cleavage of the peptide C-N bond follows with the amine being released in its protonated form. The Glu143 again abstracts a proton from water. The catalytic cycle is closed by detachment of the carboxyl product, probably by the uptake of the incoming water molecule.

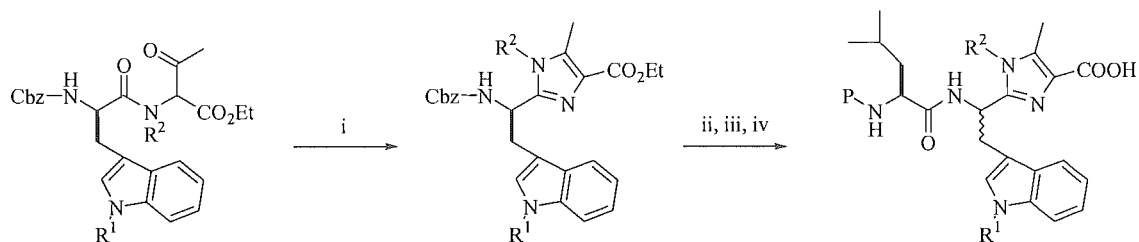
Other examples of biologically active mimetics containing C-terminal imidazoles are potent and bioavailable endothelin-A (ETA) receptor antagonists (Table 4.1).<sup>3</sup> Endothelin,<sup>4</sup> a 21-amino acid bicyclic peptide, is a very powerful constrictor of vascular smooth muscle, as well as a potent mitogen. It has been reported as a pathogenic factor for a variety of diseases, including asthma,<sup>5a</sup> coronary vasospasm, myocardial infarction,<sup>5b</sup> pulmonary hypertension,<sup>5c</sup> restenosis,<sup>5d</sup> and atherosclerosis.<sup>5e</sup> Endothelin acts by binding to a family of membrane associated, G-protein-coupled receptors.<sup>6</sup> There are two subtypes of endothelin receptors i.e. ETA and ETB. Binding of endothelin to the ETA receptor, which is found in vascular smooth muscle cells, triggers vasoconstrictive and proliferative responses. Von Geldern *et al.* have reported the synthesis and SARs results of the highly potent and well-absorbed C-terminal imidazole based ETA receptor agonists,<sup>3</sup> which are summarised in Table 4.1.

Table 4.1: Activity of C-terminal imidazole based endothelin antagonists

Entry	P	R <sup>1</sup>	R <sup>2</sup>	ETA binding IC <sub>50</sub> (μM) <sup>a</sup>
1		Me	H	0.011
2		H	H	0.57
3		Me	H	0.28
4		H	Me	23.3
5		H	Bn	16.2

a: IC<sub>50s</sub> calculated for 11 concentrations from 10<sup>-10</sup> to 10<sup>-5</sup> M.

Von Geldern *et al.*<sup>3</sup> have prepared the C-terminal imidazole mimetics by refluxing the intermediate  $\alpha$ -amido  $\beta$ -ketoesters in acetic acid and NH<sub>4</sub>OAc as outlined in Scheme 4.1 on the next page. The scope of this method is limited due to incompatibility of other *N*-protecting groups (e.g. a Boc group) to such harsh conditions used in step a, and loss of stereochemical integrity observed in the final product.<sup>3</sup>



Reagents and conditions: i)  $\text{NH}_4\text{OAc}$ ,  $\text{HOAc}$ , reflux. ii)  $\text{H}_2/10\% \text{Pd-C}$ ,  $\text{EtOH}$ . iii)  $\text{Phe-Leu-OH}$ ,  $\text{EDCl}$ ,  $\text{HOBT}$ ,  $\text{NMM}$ ,  $\text{THF}$ ,  $\text{DMF}$ . iv)  $\text{LiOH}$ ,  $\text{H}_2\text{O}$ ,  $\text{THF}$ , reflux  
 $\text{R}^1, \text{R}^2 = \text{see Table 4.1}$

Scheme 4.1: Synthesis of Imidazole mimetics using  $\text{NH}_4\text{OAc}$  and  $\text{HOAc}$ .

C-terminal imidazole mimetics have been utilized as stable isosteres in peptidomimetics of medicinal importance. For example introduction of the imidazole ring as replacement of the amide bond in **4.1** reduces its peptidic character and thus increasing its bioavailability as HIV protease inhibitor<sup>7</sup> (Figure 4.3).

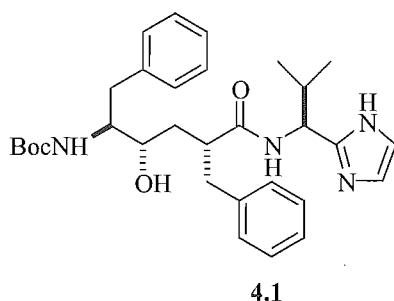
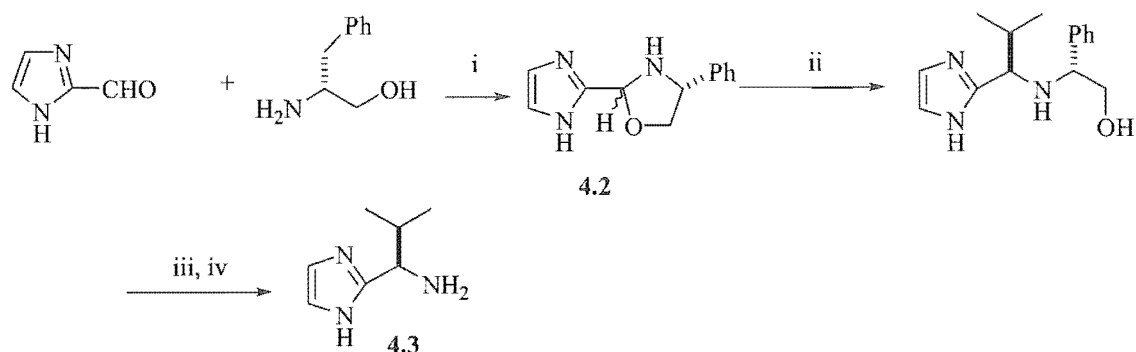


Figure 4.3: **4.1** contains a C-terminal imidazole ring.

The Val based C-terminal 2-functionalized imidazolinium component of **4.1** is prepared by adding nucleophilic organometallics to non-racemic 2-oxazolidinones using 2-phenylglycinol as the source of chirality as depicted in Scheme 4.2.

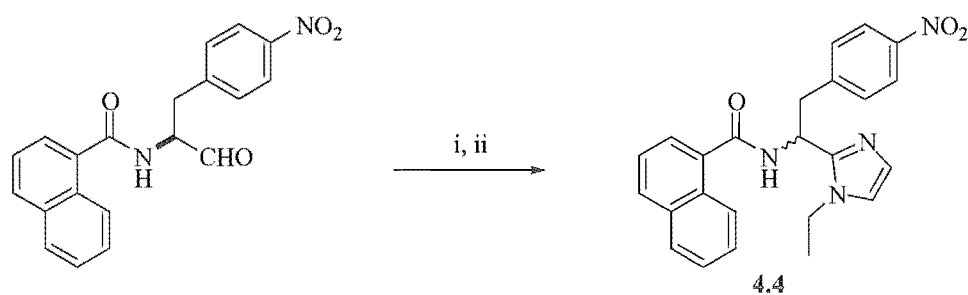


Reagents and conditions: i) Toluene, MS. ii) *i*-PrCeCl<sub>3</sub>, THF. iii) HCl. iv) Pb(OAc)<sub>4</sub>

Scheme 4.2: Synthesis of C-terminal Val-based imidazole **4.3**.

This method employs the imidazole carboxaldehyde as the starting material and uses uncommon Ce organometallics. The synthesis of **4.3** by the typical method of reacting (*S*)-valinal with NH<sub>3</sub> in glyoxal trimer hydrate, with retention of configuration at the chiral centre, has also been published in the same report.

Dhanak and co-workers have synthesized of 2-functionalized single amino acid C-terminal imidazole mimetic **4.4** as CCR3 receptor antagonists (Scheme 4.3).<sup>8</sup>



Conditions : i) NH<sub>3</sub>, glyoxal, DMF. ii) aq. KOH, EtI, DMF.

Scheme 4.3: Synthesis of racemic phenylalanine derived C-terminal imidazole **4.4**.

Problems regarding racemization have been reported during the preparation of phenyl alanine derived C-terminal imidazole mimetic **4.4** by the typical procedure of reacting (*S*)-phenyl alaninal with  $\text{NH}_3$  in glyoxal, and subsequent alkylation in the presence of KOH with EtI (Scheme 4.3).

The results obtained by Dhanak *et al.*<sup>7</sup> using  $\text{NH}_3$  and glyoxal for the synthesis of C-terminal imidazole mimetics show epimerization of imidazole, whereas Predgen *et al.*<sup>8</sup> have reported the retention of configuration using the same protocol. This vagueness in the results obtained by two groups<sup>7,8</sup> limits the generality of this method. Therefore, the development of a general and reliable method of synthesis of non-racemic C-terminal imidazole mimetics using mild reactions, and compatible with a variety of *N*-protecting groups seems crucial.

Haberhauer *et al.* have reported the synthesis of imidazole-containing cyclopeptide **4.1b-c** as analogue of the naturally occurring **4.1a**.<sup>9</sup> Other heterocycles such as oxazole, thiazole, oxazoline and thiazoline are found in nature in *lissoclium* class of cyclopeptides (e.g. westiellamide **4.1a**) obtained from marine sources<sup>9</sup> (Figure 4.4).

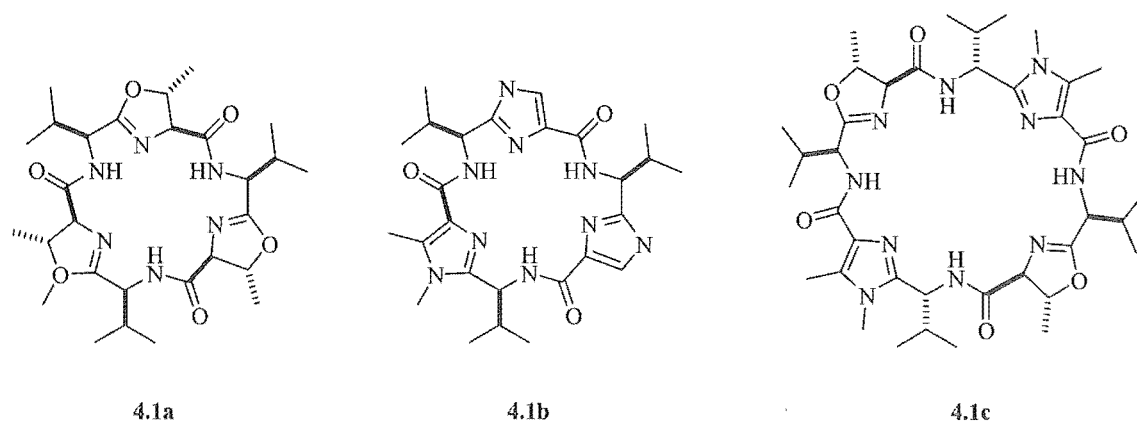


Figure 4.4: *Lissoclium* cyclopeptide **4.1a** and its imidazole analogue **4.1b** and **4.1c**.

The synthesis of non-peptide imidazole-based antagonists of the Angiotensin receptor as potent antihypertensives has been reported by Carini *et al.*<sup>10</sup> (Figure 4.5). Angiotensin II, an octapeptide produced by the renin-angiotensin system, is a powerful endogenous vasopressor. Renin-angiotensin inhibitors have been found to be effective for the treatment of human hypertension. These angiotensin converting enzyme (ACE) inhibitors work by blocking the production of angiotensin II from angiotensin I.

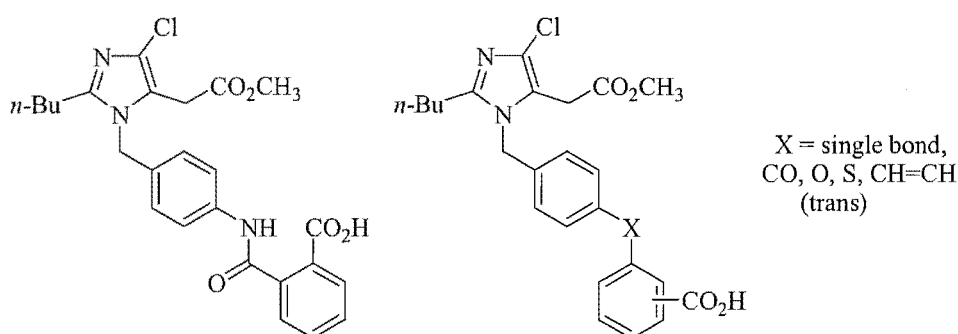
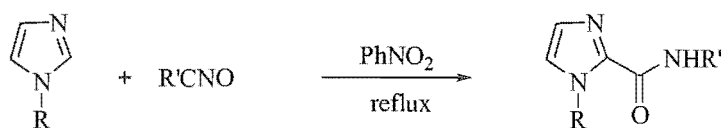


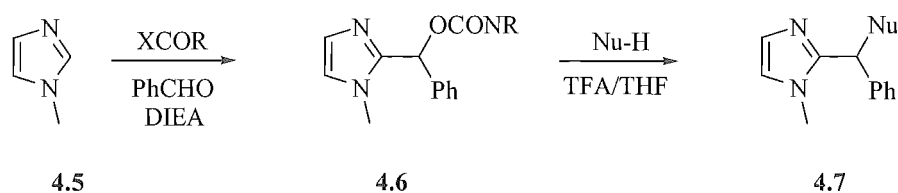
Figure 4.5: Derivatives of imidazoles as potent hypertensive agents.

A conventional method for the preparation of 2-substituted aliphatic imidazoles uses the reaction of imidazole with an electrophile (e.g. an aldehyde<sup>11a</sup> or isocyanate,<sup>11b</sup> Scheme 4.4).



Scheme 4.4: Synthesis of 2-substituted imidazoles by the reaction of imidazole and isocyanate.

Recently, Halsta *et al.* have reported a synthon of 2-substituted aliphatic imidazoles by treating an azolium ylide with reactive carbamoyl and carbonyl compounds.<sup>12</sup> Subsequent solvolysis of 4.6 gives 2-substituted imidazoles containing a variety of substituents (Scheme 4.5).

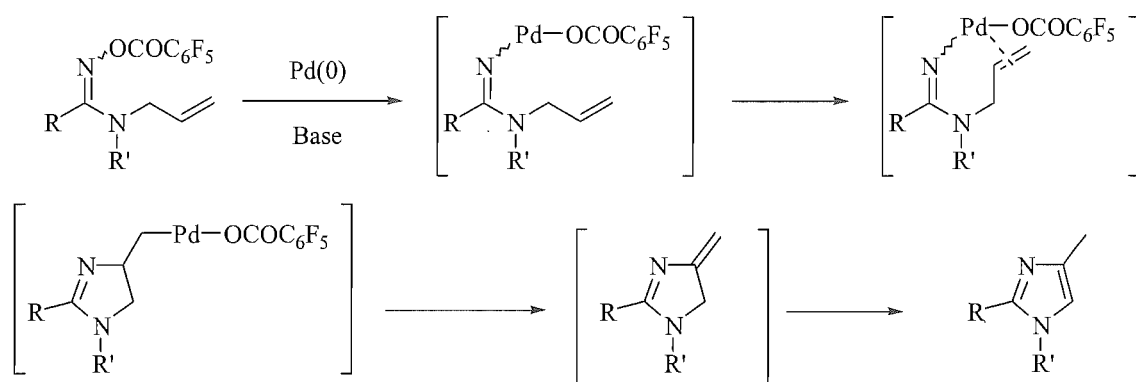


Scheme 4.5: Acylation of imidazole 4.5 and solvolysis reaction of 4.6 to give 4.7.

The diverse applications of imidazole-containing compounds, have made them attractive targets for organic and medicinal chemists. Significant efforts have thus gone into developing new and efficient methods for the synthesis and functionalization of simple and amino acid-based non-racemic imidazoles. We have developed a general Pd-catalyzed methodology involving application of A-H reaction to the synthesis of 1,2,4-substituted imidazoles. What follows is a discussion about the synthetic strategy and results obtained from the synthesis of aliphatic and non-racemic amino acid-based imidazoles.<sup>13</sup>

## 4.2 Synthetic Plan for the Synthesis of Aliphatic and C-terminal Amino Acid Imidazoles

The proposed synthetic strategy for the synthesis of imidazoles was based on an A-H cyclization of *O*-pentafluorobenzoyl *N*-alkyl, *N*-allyl amidoximes. Oxidative addition of Pd(0) to the N-O bond of the *O*-pentafluorobenzoyl amidoxime would occur to give an alkylideneamidopalladium(II) species which would add to the olefinic side chain. Elimination of a palladium hydride species would then give a dihydroimidazole, which would finally isomerise under reaction conditions to the imidazole (Scheme 4.6).



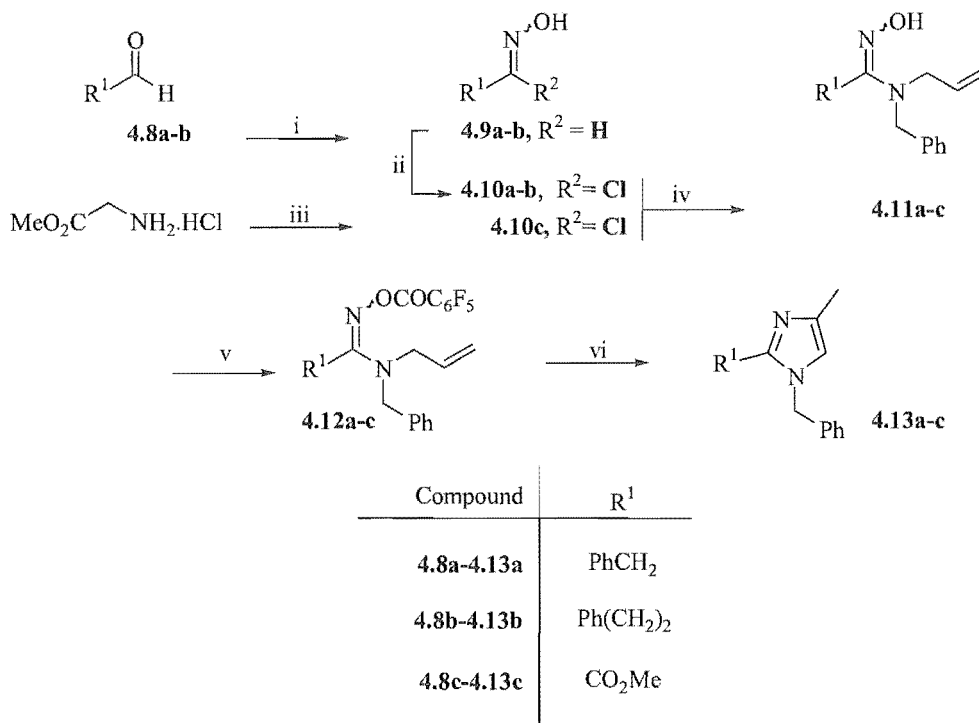
Scheme 4.6: Synthetic plan for the synthesis of imidazoles.

### 4.3 Synthesis of Imidazoles from Aliphatic Aldehydes

The synthetic steps involved in the synthesis of imidazoles **4.13a-c** are outlined in Scheme 4.7. Reaction of aliphatic aldehydes **4.8a-b** with hydroxylamine, in the presence of pyridine, gave the aldoximes **4.9a**<sup>14a</sup> (1:1, 75%) and (*E/Z*) **4.9b**<sup>14b</sup> (3:2, 72%), respectively. These were then separately treated with NCS in dry DMF at 70 °C, to give the corresponding hydroxamoyl chlorides **4.10a-b**, which were coupled *in situ* with *N*-allyl benzyl amine<sup>15</sup> in DMF to give predominantly **4.11a** (63%) and **4.11b** (61%) as single isomers, tentatively assigned as the *E*-configuration.<sup>†</sup> In a separate experiment, **4.9b** was treated with NCS and the crude product isolated and analysed by <sup>1</sup>H NMR to show **4.10b** as a single isomer, characterized and tentatively assigned the *E*-configuration. The sample of **4.10b** was then reacted with *N*-allyl benzyl amine as per the *in situ* experiment to give the identical isomer of **4.11b**. Modeling studies of the (*E/Z*)-amidoximes **4.11a-b** also suggested the population of the amidoximes **4.10a-b** to be in the lower energy (*E*)-conformation. This is attributed to the intramolecular  $\pi$ -H bonding between the electron deficient oxime hydrogen (C=NOH) and the electron-rich phenyl rings.

<sup>†</sup> *O*-alkyl hydroxamoyl chlorides are reported to isomerise to the thermodynamically stable *E*-isomers,<sup>16</sup> and that these react stereospecifically to give *E*-amidoximes.<sup>17</sup>





Reagents and conditions: i) NH<sub>2</sub>OH.HCl, pyridine, EtOH, rt. ii) NCS, DMF, 70° C, 2h. iii) NaNO<sub>2</sub>, HCl, H<sub>2</sub>O, -5° C.

iv) allyl benzyl amine, DMF, 70° C. v) C<sub>6</sub>F<sub>5</sub>COCl, TEA, DCM, 0° C. vi) Pd(PPh<sub>3</sub>)<sub>4</sub>, TEA, DMF, 80° C.

Scheme 4.7: Synthesis of imidazoles 4.13a-c.

Similarly, aliphatic hydroxamoyl chloride **4.10c** prepared as an (*E/Z*) mixture (6:5) from glycine methyl ester hydrochloride<sup>18</sup> (Scheme 4.7), was also treated with *N*-allyl benzyl amine to give **4.11c** (75%) as a 6:5 mixture of isomers. Modeling for (*EZ*)-**4.11c** suggested that low energy conformers exhibit  $\pi$ -H bonding between the oxime OH and the electron rich double bond suggesting **4.11c** as *Z*-configured. However, experimentally both *E* and *Z* isomers are observed for **4.11c** suggesting that intramolecular H bonding might also be displayed between the hydroxyl H and either oxygen of the methyl ester group.

The substrates for A-H reaction (**4.12a-c**) were then prepared by reacting separate samples of (*E*)-**4.11a**, (*E*)-**4.11b** and (*E/Z*)-**4.11c** (6:5) with TEA and pentafluorobenzoyl chloride

in DCM at 0 °C to give (*E*)-**4.12a-b** as single isomers and (*E/Z*)-**4.12c** (4:1) in 83, 87 and 88% yields respectively. An *N,O*-pentafluorobenzoyloxime was chosen for A-H sequence since this group is known to suppress the competing Beckmann rearrangement.<sup>13d</sup> Modeling studies for **4.12a** and **4.12b** suggested the *E* isomers of lowest energy, which is likely due to  $\pi$ - $\pi$  stacking between the pentafluorophenyl and the 2-substituted phenyl(methyl) and phenyl(ethyl) groups for **4.12a** and **4.12b** respectively. Low energy conformations for **4.12c** (4:1) also display  $\pi$ - $\pi$  stacking between the phenyl ring of the benzyl group and the pentafluorophenyl ring, suggesting *Z* configuration for the major isomer. Assignment of the *E/Z* isomer ratios of the amidoximes and pentafluorobenzoyloximes is thus, tentatively based on computer modeling as explained further in section 4.5.

The *N,O*-pentafluorobenzoyl amidoximes **4.12a-b** were treated with 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> and 5 equivalents of TEA in DMF, at 80° C for 30 minutes, to give the desired imidazoles **4.13a-b** in 72% and 70% yields respectively. The A-H cyclization of **4.12c** was slow requiring 3 h to give 30% of the corresponding imidazole **4.13c**. The lower yield in this case is unlikely to be linked to the presence of two isomers in the substrate **4.12c**, since the A-H reaction has been reported to be independent of the geometry of the oxime.<sup>13d</sup>

The imidazoles were characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. Key observations include the difference in chemical shifts for the equivalent C-4 CH<sub>3</sub> protons for **4.13a-c** is ~0.04 ppm as depicted in Figure 4.6. Other key equivalent protons are C-1 benzylic protons which appear at the same chemical shift for **4.13a** and **4.13b** whereas chemical shift for the same protons in **4.13c** is shifted 1.71 ppm downfield due to the proximity of electron withdrawing ester group (see Figure 4.6). The difference in chemical shifts for C-5 olefinic proton is ±0.24 ppm, and shows the same trend as for C-1 benzyl protons.

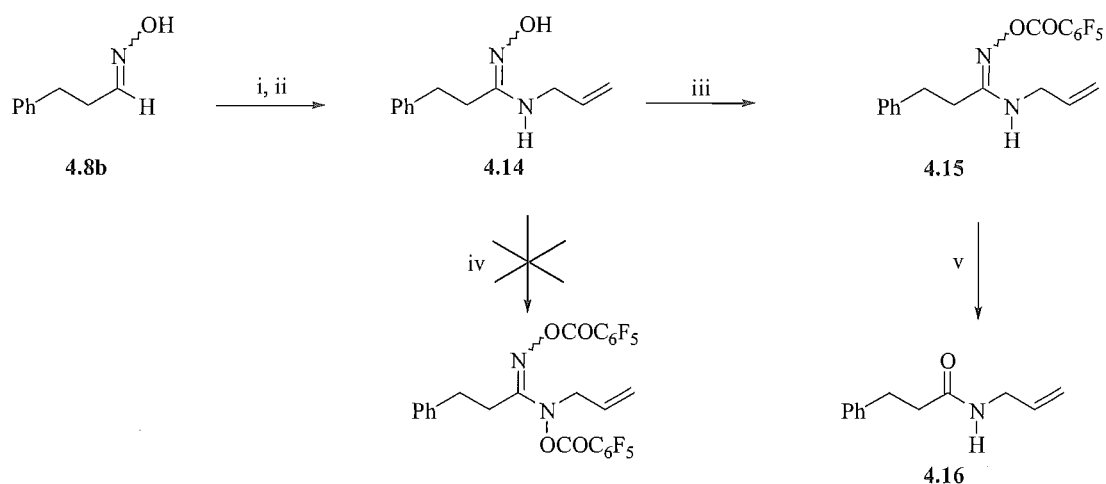
R = PhCH<sub>2</sub>, Ph(CH<sub>2</sub>)<sub>2</sub>, CO<sub>2</sub>Me

Compound	CH <sub>3</sub>	Benzyl-H	H-5
<b>4.13a</b>	2.22	4.80	6.52
<b>4.13b</b>	2.23	4.80	6.50
<b>4.13c</b>	2.18	5.51	6.74

Figure 4.6: Comparison of the chemical shifts of 4-CH<sub>3</sub>, 1-CH<sub>2</sub> and 5-CH protons for the imidazoles **4.13a-c**

The structures of the aliphatic imidazoles were further confirmed by the data obtained from 2D COSY, HSQC/DEPT and mass spectrometry.

After successfully using A-H cyclization for the synthesis of *N*-benzyl imidazoles, extension of the same methodology was attempted for the synthesis of aliphatic imidazoles containing *N*-carbamoyl substituents. *N*-Carbamoylation of allyl amine with *N*-Boc<sup>19</sup> and *N*-Cbz<sup>19</sup> groups was achieved by the literature methods. Simple allyl amine was also used to check the possibility of A-H cyclization in the absence of an *N*-substituent (Scheme 4.8). Coupling of the oxime **4.8b** could be achieved only with allyl amine to give amidoxime **4.14**, where as coupling with *N*-allyl, *N*-Boc amine and *N*-allyl, *N*-Cbz amine was not successful (Scheme 4.8). The reason for this could be the reduced nucleophilic character of the amine N atom due to the electron withdrawing effect of *t*-Boc and Cbz groups.



Reagents and conditions: i) NCS, DMF, 70 °C, 2h & then allyl benzyl amine, DMF, 70 °C. iii)  $\text{C}_6\text{F}_5\text{COCl}$ , TEA, DCM, 0 °C. iv) 2  $\text{C}_6\text{F}_5\text{COCl}$ , TEA, DCM, 0 °C. v)  $\text{Pd}(\text{PPh}_3)_4$ , TEA, DMF, 80 °C.

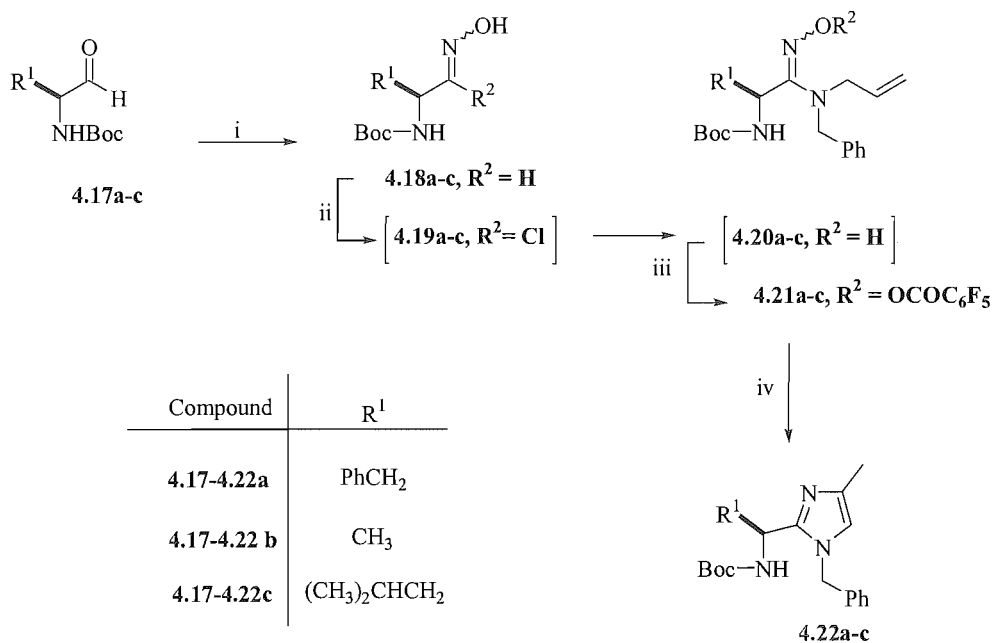
Scheme 4.8: Attempted N-substitution of 4.14 and A-H reaction of 4.15.

In addition, bi-pentafluorobenzylation of the unsubstituted amidoxime derivative 4.14 could not be achieved, as the reaction of compound 4.14 with 2 equivalents of  $\text{C}_6\text{F}_5\text{COCl}$  and TEA gave only the *O*-acylated amidoxime derivative 4.15. *N*-Carbamoylation thus seems difficult in the presence of more acidic oxime proton. A-H cyclization of the NH derivative 4.15 was attempted, but cyclization to the desired imidazole did not occur, rather 4.16 was obtained as the sole product in 80% probably via simple hydrolysis of the *O*-pentafluorobenzoate. This result suggests that the presence of *N*-substituent seems important for the A-H cyclization of amidoximes.

#### 4.4 Synthesis of Imidazoles from $\alpha$ -Amino Aldehydes

The A-H cyclization was next extended to amino acid-based examples as depicted in Scheme 4.9 below. The key starting aldehydes 4.17a-c were prepared by DIBALH reduction of (*S*)-*N*-Boc-PheOMe, (*S*)-*N*-Boc-AlaOMe, and (*S*)-*N*-Boc-LeuOMe

respectively.<sup>20</sup> Treatment of each of these aldehydes with hydroxylamine in the presence of  $\text{Na}_2\text{CO}_3$  gave  $\alpha$ -amino aldoximes<sup>20</sup> (*E/Z*)-**4.18a** (79%, 2:1), (*E/Z*)-**4.18b** (72%, 3:1), (*E/Z*)-**4.18c** (83%, 3:2) which were purified by column chromatography and recrystallisation.



Reagents and conditions:  $\text{NH}_2\text{OH}\cdot\text{HCl}$ ,  $\text{Na}_2\text{CO}_3$ , methanol/water (1:1), rt. ii)  $\text{NCS}$ ,  $\text{DMF}$ ,  $70^\circ\text{C}$ , 2h & then allyl benzyl amine,  $\text{DMF}$ ,  $70^\circ\text{C}$ . iii)  $\text{C}_6\text{F}_5\text{COCl}$ ,  $\text{TEA}$ ,  $\text{DCM}$ ,  $0^\circ\text{C}$ . iv)  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{TEA}$ ,  $\text{DMF}$ ,  $80^\circ\text{C}$ .

Scheme 4.9: Synthesis of imidazoles **4.22a-c** derived from  $\alpha$ -amino aldehydes **4.17a-c**.

A one-pot treatment of each of these oximes with  $\text{NCS}$ , as for **4.9a-b** in Scheme 4.5, gave the hydroxamoyl chlorides **4.19a-c**, which reacted *in situ* with *N*-allyl benzyl amine to give the amidoximes as mixture of isomers (*E/Z*)-**4.20a** (2:5), (*E/Z*)-**4.20b** (3:8), (*E/Z*)-**4.20c** (1:5) based on analysis of  $^1\text{H}$  NMR spectroscopy. Modeling studies conducted for **4.20a-c** suggested the *Z* isomers as major products, as they are stabilized by  $\pi$ -H bonding between oxime the OH and the double bond. These were used in the next step without further

purification. Thus, the major isomers of (*E/Z*)-**4.20a-c** were assigned as *Z*-configured based on modeling.

Treatment of (*E/Z*)<sup>†</sup>-**4.20a-c** with TEA and pentafluorobenzoyl chloride, as for **4.11a-c**, gave the substrates (**4.21a-c**) for the A-H reaction as single isomers in 61, 63 and 31% yields respectively. Pentafluorobenzoylamidoximes **4.21a-c** were obtained as single isomers from (*E/Z*)-mixture suggesting that the minor isomers might have isomerised to the thermodynamically more stable isomers. Molecular modeling suggests >98% population of **4.21a-c** in *E*-conformation stabilized by intramolecular H-bonding between a fluorine and NH group in **4.21b** and **4.21c**, and  $\pi$ - $\pi$  stacking between the pentafluorophenyl and the phenyl rings in **4.21a**. Thus, *E*-configuration was assigned temporarily to **4.21a-c** based on molecular modeling, and is discussed further in section 4.5.

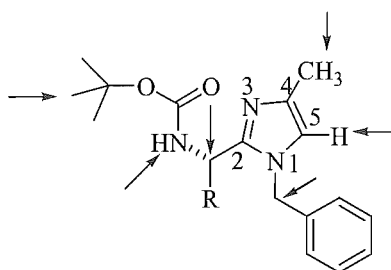
Compounds **4.21a-c** were then subjected to the amino Heck reaction conditions to give the C-terminal amino acid mimetics **4.22a-c** in good yields. In particular, the (*S*)-Phe-based amidoxime derivative **4.21a** cyclized smoothly in 1h to give the imidazole derivative **4.22a** in 70% yield, while (*S*)-Ala-based **4.22b** was isolated in 68% after a comparatively shorter reaction time of 30 min. The imidazole derivative of (*S*)-Leu **4.22c** was isolated in 56% yield after 1 h reaction. The reaction works well, with the crude NMR for all imidazoles showing a turnover of 90-95%, but the isolated yields were somewhat lowered due to difficulties in separation of the imidazoles and triphenylphosphine oxide formed from the decomposition of Pd(PPh<sub>3</sub>)<sub>4</sub> by chromatography.

The <sup>1</sup>H NMR data for compounds **4.22a-c** show that the *t*-Bu, CH<sub>α</sub>NH, 1-benzyl, 4-CH<sub>3</sub> and 5-olefinic protons exhibit the chemical shifts in the same region with a little variation.

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<sup>†</sup> The assignment of isomers is ambiguous and unimportant as both isomers react in the A-H reaction.<sup>13d</sup> However, Sauve *et al.* suggested for  $\alpha$ -amino amidoximes the *Z*-isomer to be predominant.<sup>21</sup>

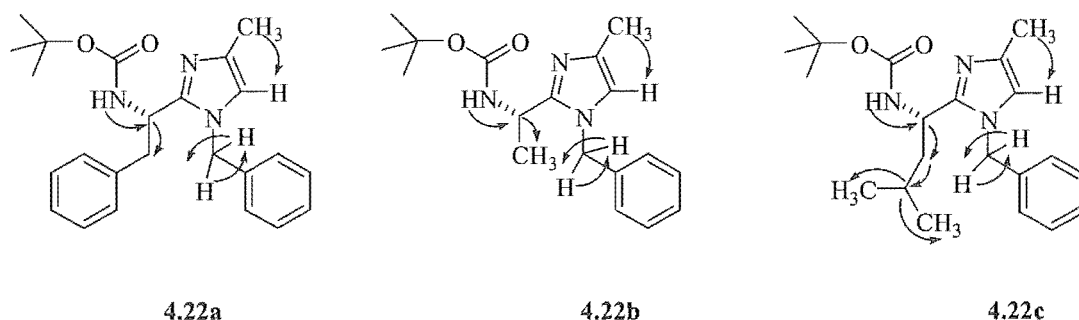
Figure 4.7 depicts a comparison of the key  $^1\text{H}$  NMR resonances for **4.22a-c**. The nine  $\text{CH}_3$  protons of the *t*-Bu group appear in the same region  $\sim 0.02$  ppm different from each other. The difference in chemical shift for the  $\text{CH}_\alpha$  proton is  $\sim 0.09$  ppm whereas the variation in chemical shifts for NH is  $\sim 0.39$  ppm. Similar to the aliphatic imidazoles, the  $\text{CH}_3$  protons at C-4 appear approximately at the same position ( $\sim 2.2$  ppm) with a negligible difference of 0.01 ppm. The benzyl protons for **4.22a** appear at 4.67 ppm as a singlet whereas, for **4.22b-c**, these appear as doublet of doublets between 5.08-5.11 and 5.16-5.22 ppm. The olefinic proton appear as a multiplet between 6.35 and 6.52 ppm. All these results confirm the structures of imidazoles **4.22a-c**.



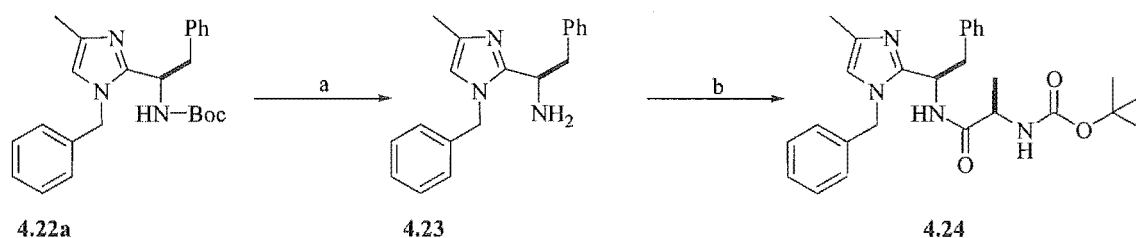
Compound	<i>t</i> -Bu	$\text{CH}_\alpha$	NH	$\text{CH}_3$	Benzyl-H	H-5
<b>4.22a</b>	1.36	4.95	5.44	2.20	4.67	6.35
<b>4.22b</b>	1.39	4.91	5.27	2.19	5.08/5.16	6.52
<b>4.22c</b>	1.38	4.86	5.05	2.19	5.11/5.22	6.52

Figure 4.7: Comparison of the chemical shifts of *t*-Bu,  $\text{CH}_\alpha$ , NH, 4- $\text{CH}_3$ , 1- $\text{CH}_2$  and 5-CH protons for the imidazoles **4.22a-c**.

Figure 4.8 depicts key 2D-COSY correlations for imidazoles **4.22a-c**, whose structures were further proved by 2D HSQC/DEPT,  $^{13}\text{C}$  NMR and mass spectrometry.

Figure 4.8: Key 2D-COSY connectivity data for **4.22a-c**.

Optical rotations were measured for **4.22a-c** with  $[\alpha]_D^{20}$  of  $-8.3^\circ$ ,  $-74.2^\circ$  and  $-54.3^\circ$  respectively. The optical purity of the (*S*)-Phe-based imidazole **4.22a** was checked by removing the *N*-Boc group using 1N HCl in EtOAc (Scheme 4.10) at rt to give the free amine **4.23** (100%). Compound **4.23** was then coupled with (*S*)-*N*-Boc alanine under standard peptide coupling conditions using EDCI, HOBT and DIPEA to give **4.24** (> 95% *de*, based on analysis of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra). This result suggests that little or no racemization has occurred in the preparation of the imidazole.



Reagents and conditions: a) 1N HCl, EtOAc, rt, 3h. b) *N*-*t*-Boc L-Alanine, EDCI, HOBT, DIPEA, DMF, rt, 16h.

Scheme 4.10: Deprotection of Boc from **4.22a** and synthesis of **4.24**.



## 4.5 Modeling Studies for Assignment of Configuration to the Amidoximes and their *O*-pentafluorobenzoyl Derivatives

The *E/Z* configuration of aliphatic and amino acid-based amidoximes and their *O*-pentafluorobenzoyl derivatives were tentatively assigned on the basis of modeling studies. The MacroModel molecular mechanics programme OPLS2001 forcefield in CHCl<sub>3</sub> was used for minimization and conformational study. The Clustering programme X cluster was subsequently used for sorting and identification of *E* and *Z* isomers. Each compound was minimized in CHCl<sub>3</sub> by the PRCG method converging on a gradient with a threshold of 0.05 kJ mol<sup>-1</sup>Å<sup>-1</sup>. Each compound was then subjected to a conformational search using the MCMM method. Conformers within 21 kJ were saved after 5000 steps. The ensemble of each conformer was then subjected to cluster analysis. The comparison atoms used for clustering were the oxime C, N and O, plus the adjacent C and N atoms on each side.

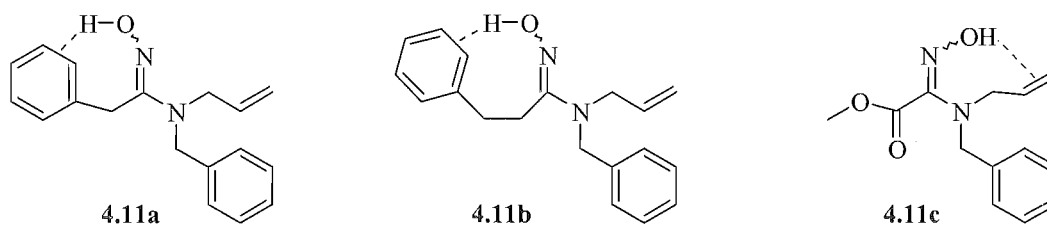
### 4.5.1 Stereochemistry of Aliphatic Amidoximes and *O*-pentafluorobenzoylamidoximes

Table 4.2 highlights the Boltzmann weighted energy (which reflects the relative thermodynamic stability) of each isomer for the aliphatic amidoximes and the pentafluorobenzoylamidoximes from the modeling studies, which indicates that the low energy conformers for **4.11a-b** have *E* configuration.

Table 4.2: Boltzmann weighted energy of *E*:*Z* ratio for **4.11a-c** and **4.12a-c**.

Compound	<b>4.11a</b>	<b>4.11b</b>	<b>4.11c</b>	<b>4.12a</b>	<b>4.12b</b>	<b>4.12c</b>
Boltzmann weighted % of <i>E</i>	94.5	76.3	0	100	100	0.5
Boltzmann weighted % of <i>Z</i>	4.6	23.7	100	0	0	99.5

This may be attributed to the fact that there is less steric bulk on that side, and the oxime OH also displays a  $\pi$ -H bond with electron rich phenyl rings in **4.11a-b** as shown in Figure 4.9.

Figure 4.9:  $\pi$ -H bonding detected by modeling for **4.11a-c**.

In contrast, low energy conformers for **4.11c** suggest a 100% *Z* configuration stabilized by a  $\pi$ -H bond between the oxime OH and the double bond.

The experimental data for the *major:minor* isomers of **4.11-4.12a-c** are summarized in Table 4.3, which show that **4.11a-b** were obtained as single isomers (based on analysis of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy), and were assigned as *E*-configuration based on modeling studies.

Compound	4.11a	4.11b	4.11c	4.12a	4.12b	4.12c
<i>major</i>	100	100	6	100	100	4
<i>minor</i>	0	0	5	0	0	1

$(E)$  - 4.10b

$(E)$  - 4.11b

The structures of global minima for (*E*)-4.11a and (*Z*)-4.11c are represented in Figure 4.10.

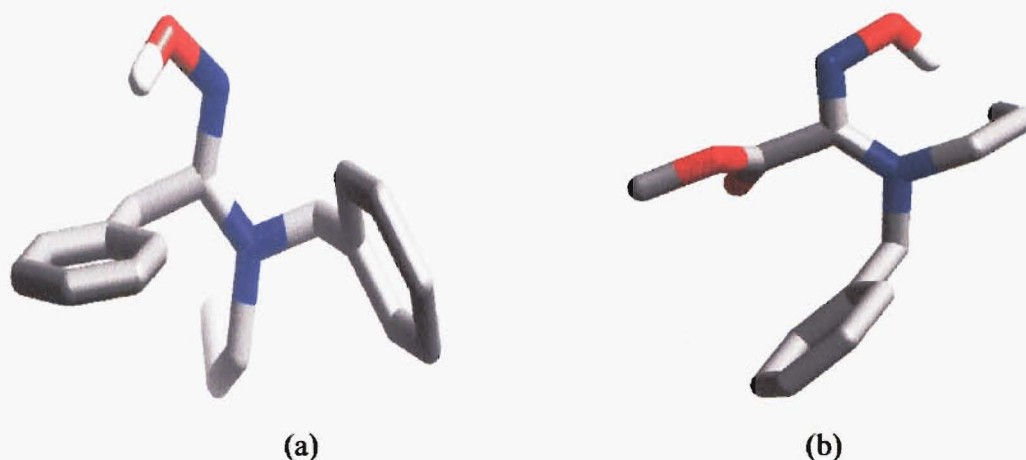


Figure 4.10: Structure of global minima of **4.11a** (a) and **4.11c** (b).

The *O*-pentafluorobenzoates **4.12a-b** were obtained as single isomers (determined by  $^1\text{H}$  NMR) and were assigned *E*-configuration based on modeling, which revealed that the low energy conformers have an *E*-configuration. This might be due to less steric bulk on that side and possible  $\pi$ - $\pi$  stacking between phenyl and pentafluorophenyl rings as indicated by the dotted lines in Figure 4.11.

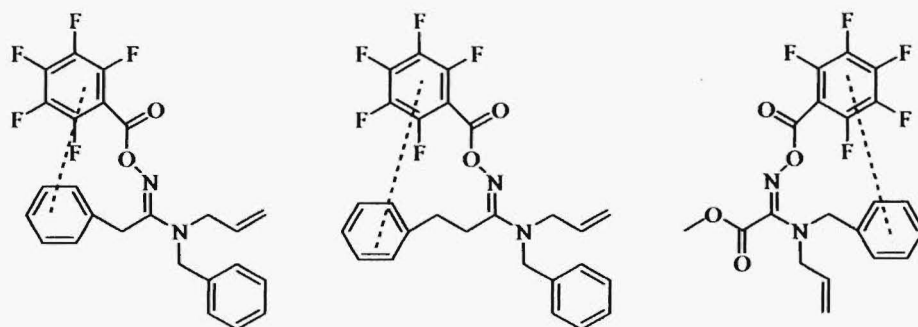
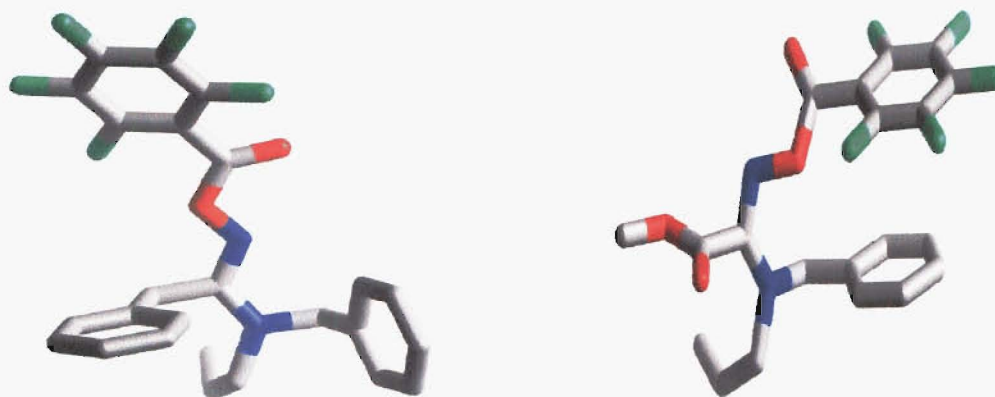


Figure 4.11:  $\pi$  -  $\pi$  stacking between the phenyl rings in *E* - **4.12a-b** and *E* - **4.12c**

Modeling suggested **4.12c** predominantly to have *Z* configuration. However, the experimental data shows two isomers in a 4:1 ratio (established by  $^1\text{H}$  NMR). The major

isomer was assigned as *Z* to represent the modeling results, as the low energy conformers of **4.12c** show the  $\pi$ - $\pi$  interaction between the pentafluorophenyl and the phenyl ring of the *N*-benzyl group. Figure 4.12 represent structures of the global minima of *E*-**4.12a** and *Z*-**4.12c**.

Figure 4.12 (a) **4.12a**(b) **4.12c**

#### 4.5.2 Stereochemistry of Amino Acid-based Amidoximes and *O*-pentafluorobenzoyl-amidoximes

Table 4.4 summarizes the Boltzmann weighted energy (representing the relative thermodynamic stability) of each isomer for the amino acid-based amidoximes **4.20a-c** and the pentafluorobenzoylamidoximes **4.21a-c** obtained from modeling.

Table 4.4: Boltzmann weighted energy of *E*:*Z* ratio for **4.20a-c** and **4.21a-c**.

Compound	<b>4.20a</b>	<b>4.20b</b>	<b>4.20c</b>	<b>4.21a</b>	<b>4.21b</b>	<b>4.21c</b>
Boltzmann weighted % of <i>E</i>	5.9	20.5	16.8	98.7	98.2	99.6
Boltzmann weighted % of <i>Z</i>	94.1	79.5	83.2	1.3	1.8	0.4

In contrast to the aliphatic amidoximes, the relative thermodynamic stability for **4.20a-c**, decreases from 94.1 for **4.20a** to 83.2 for **4.20c** and further diminishes to 79.5 for **4.20b** as the side chain group becomes progressively smaller from **4.20a**  $\rightarrow$  **c**  $\rightarrow$  **b**. This may be attributed to the fact that there is less steric bulk on that side and the oxime OH also display a  $\pi$ -H bond with the electron rich double bond as shown in Figure 4.13.

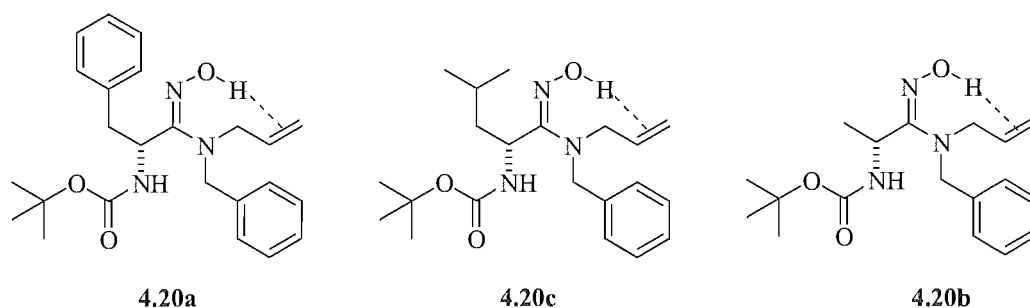


Figure 4.13:  $\pi$ -H bonding detected by modeling for **4.20a-c**.

The experimental results for **4.20a-c** and **4.21a-c** are summarized in Table 4.5, which show the ratio of *major:minor* isomers for **4.20a-c** and **4.21a-c**.

Table 4.5: Experimentally obtained *major:minor* ratio for **4.20a-c** and **4.21a-c**.

Compound	<b>4.20a</b>	<b>4.20b</b>	<b>4.20c</b>	<b>4.21a</b>	<b>4.21b</b>	<b>4.21c</b>
<i>major</i>	5	8	5	100	100	100
<i>minor</i>	2	3	1	0	0	0

Thus, the major isomers were assigned *Z* stereochemistry based on modeling results discussed earlier. The assignment of *Z* stereochemistry to the major isomer is further supported by an article published by Sauve *et al.*,<sup>21</sup> who have reported the formation of *Z*-isomers as the major isomer in their synthesis of amino acid-based amidoximes.

Compared to the aliphatic hydroxamoyl chlorides **4.10a-b**, the substituent priorities for *N*-Boc protected  $\alpha$ -amino hydroxamoyl chlorides are different, as the oxime OH group would prefer a *trans* stereochemistry to the bulky sidechain group and Boc group (Figure 4.14).

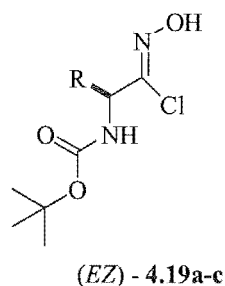


Figure 4.14: Stereochemically more favourable (*Z*)-hydroxamyl chlorides

The pentafluorobenzoylamidoximes **4.21a-c** were formed as single isomers [from (*E/Z*)-mixture of the substrates] as shown in Table 4.4, whereas modeling suggested that >98% of the thermodynamically stable, low energy conformers have *E* configuration. This may be attributed to H-bonding observed between the NH and F of the pentafluorophenyl ring in **4.21b-c**, and  $\pi$ - $\pi$  stacking between the phenyl and pentafluorophenyl rings in **4.21a** (Figure 4.15). Thus, these were assigned *E* configuration tentatively.

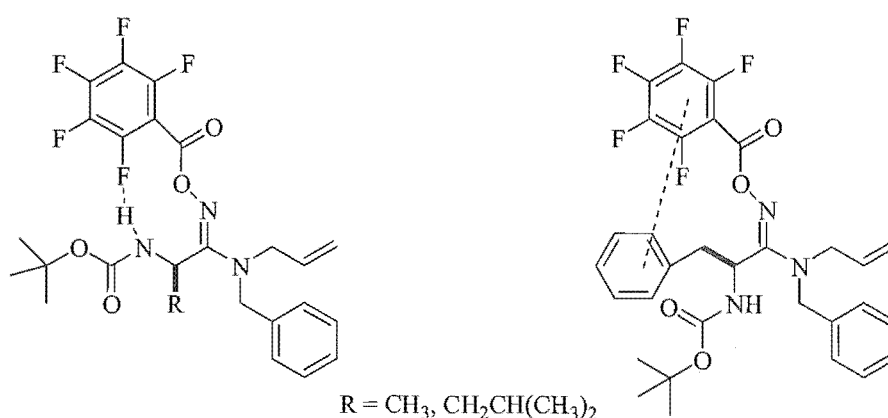
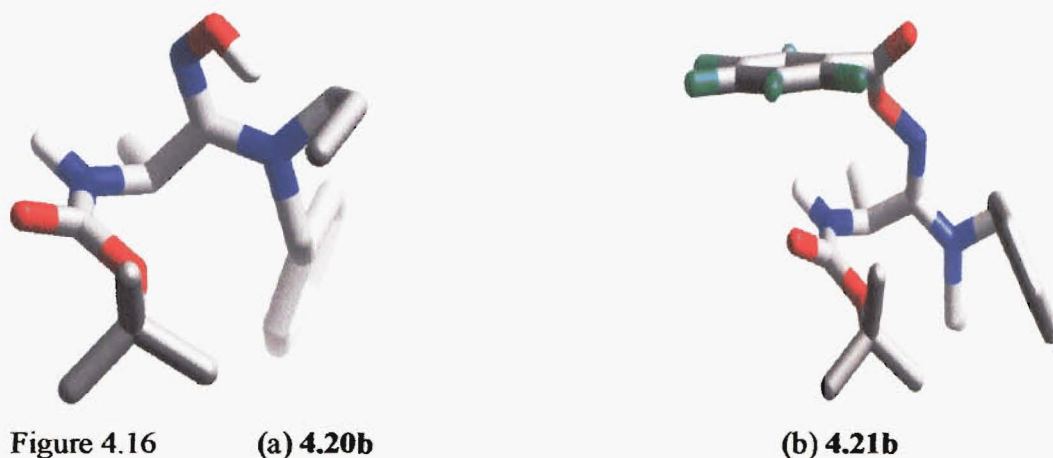


Figure 4.15: Formation of hydrogen bond between F and NH in *E* - **4.21b-c** and  $\pi$  -  $\pi$  stacking between the two rings in *E* - **4.21a**

The structure of the global minima for (*E*)-**4.20b** and (*Z*)-**4.21b** are depicted in Figure 4.16



## 4.6 Conclusion and Future Work

In summary, a new synthesis of imidazoles from aliphatic and amino acid-based aldehydes has been developed.<sup>22</sup> The sequence utilized metal-catalyzed Amino-Heck reaction to form the cyclic compounds. The imidazolyl mimetics were characterized using  $^1\text{H}$ ,  $^{13}\text{C}$  NMR and mass spectrometry. The reaction works well and both aliphatic and optically active C-terminal imidazole mimetics are formed in good yields. The C-terminal imidazole mimetics have the potential for use as *cis* amide bond replacement using A-H methodology. In addition, attempts were made to prepare 2-substituted imidazoles other than benzyl substituents; and the presence of an N-substituent has been found to be crucial for A-H cyclization (to avoid the competing Beckmann rearrangement).

Future work could involve extension of the A-H reaction to the synthesis of C-terminal di- and tripeptide imidazole derivatives. Synthesis leading to the incorporation of a second amino acid residue at N(1) of the imidazole could also be achieved by using an amine bearing a protected carboxyl group in the coupling reaction of an oxime and amine, which in turn could be coupled to the N-terminus of an other amino acid.



#### 4.7 References for chapter 4

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**CHAPTER FIVE**

**SYNTHESIS OF**  
**2-ARYL 5-FUNCTIONALIZED PYRROLES VIA**  
**AMINO-HECK REACTION FOLLOWED BY OTHER**  
**DOMINO PROCESSES**

## 5.1 Introduction

Pyrroles<sup>1</sup> are abundant as constituents of natural products and have found broad synthetic utility in both medicine and material science. The unique properties of pyrrole-containing compounds and their ubiquity in nature has thus inspired a significant interest in the synthesis of such compounds. The generality of the amino-Heck cyclization, coupled with other domino processes, has been extended to the synthesis of 2,5-disubstituted pyrroles from propargylic derivatives of *N,O*-pentafluorobenzoyl oximes. What follows is a brief introduction about the applications of pyrrole-containing compounds and methods of their synthesis.

The pyrrole ring has found great use in the design and development of pharmaceuticals. Pyrrole-containing compounds display interesting biological properties including antipsychotic (e.g. **5.1**, Figure 5.1),<sup>2</sup> anti-inflammatory (e.g. **5.2**, Figure 5.1),<sup>3</sup> radioprotective,<sup>4</sup> and spasmolytic activity.<sup>5</sup> Other drugs that possess the pyrrole moiety as an essential component include the non-steroidal anti-inflammatory agents<sup>6</sup> (e.g. **5.3** and **5.4**), and cholesterol lowering agent<sup>7</sup> **5.5**.

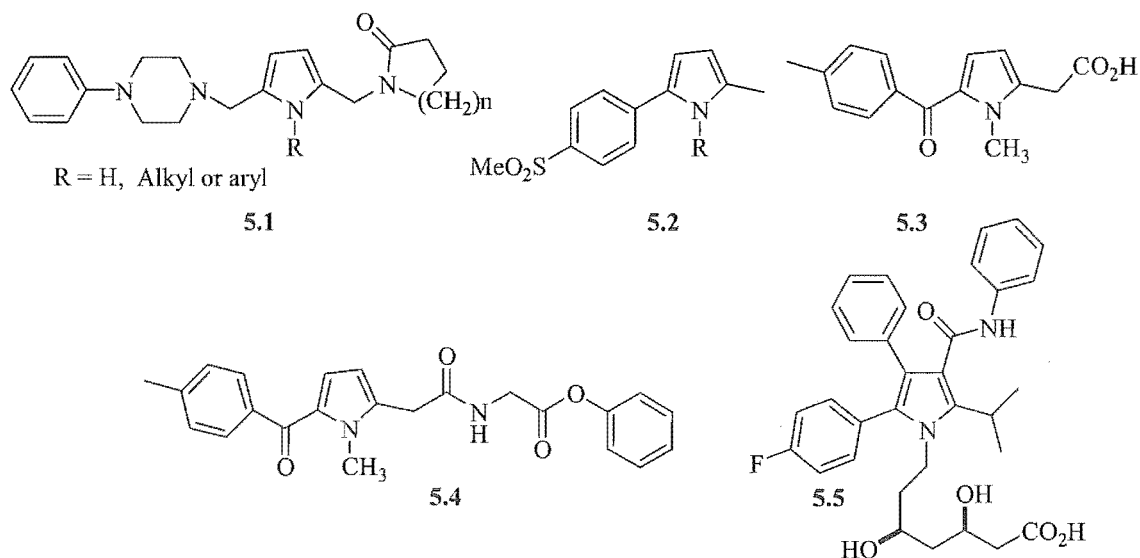


Figure 5.1: Representative pyrrole-containing drugs.

The pyrrole is a basic substructure of various natural products (see Figure 5.2). Novel applications of pyrrole containing natural products include bacterial metabolites (e.g. chromoxymicin **5.6** found in *S. rubropurpureus*),<sup>8</sup> fungal metabolites (e.g. lycogarubin A **5.7** secreted by *lycogala epidendrum*, exhibiting some anti-HSV-1 viral activity),<sup>9</sup> metabolites of marine origin (e.g. agelasine G **5.8** exhibiting antileukemic activity obtained from Okinawan *Agelas* sponge<sup>10</sup> and manzacidin C **5.9** obtained from *hymeniacidon* sponge),<sup>11</sup> and bilirubin **5.10** found in bile and gallstones.

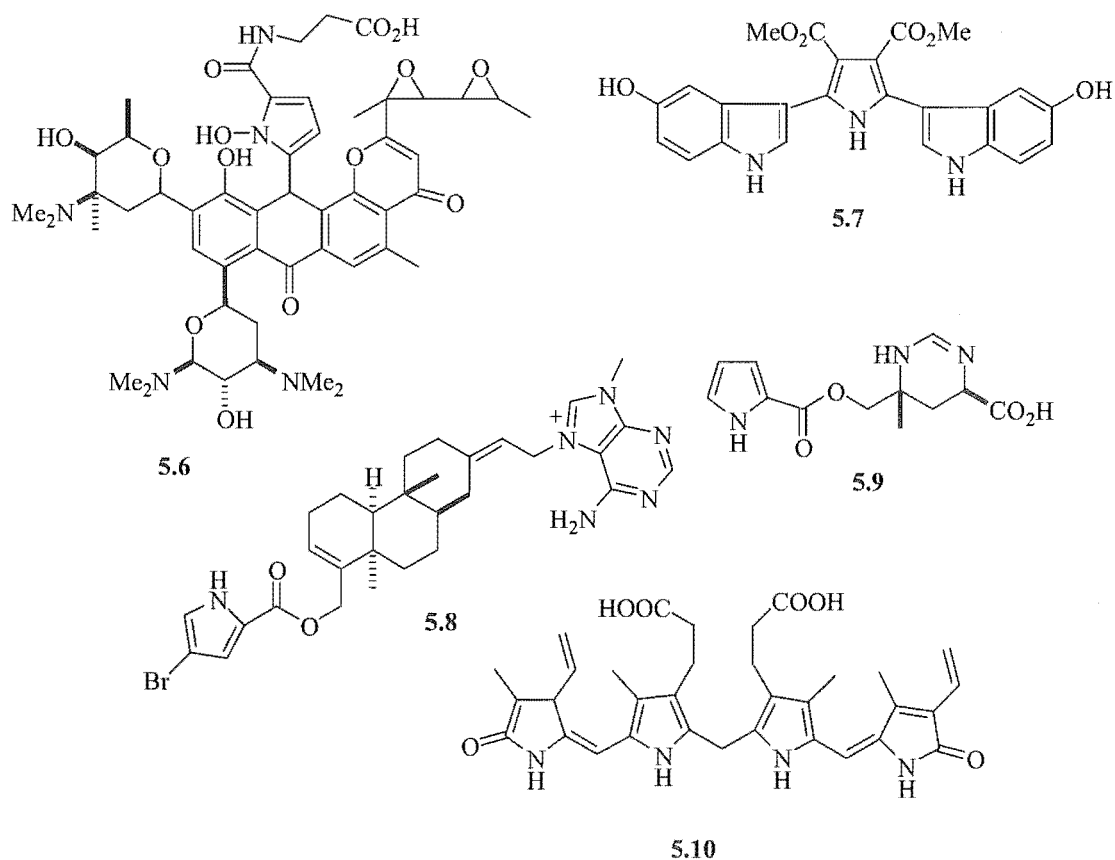
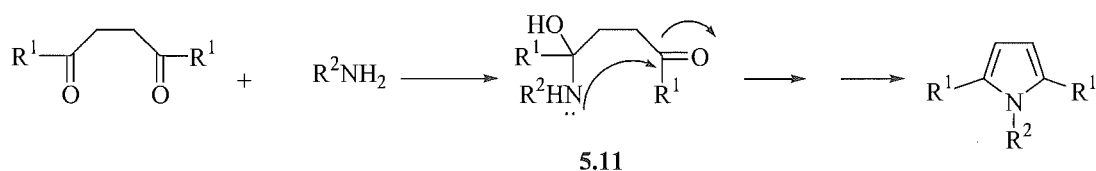


Figure 5.2: Pyrrole-containing natural products.

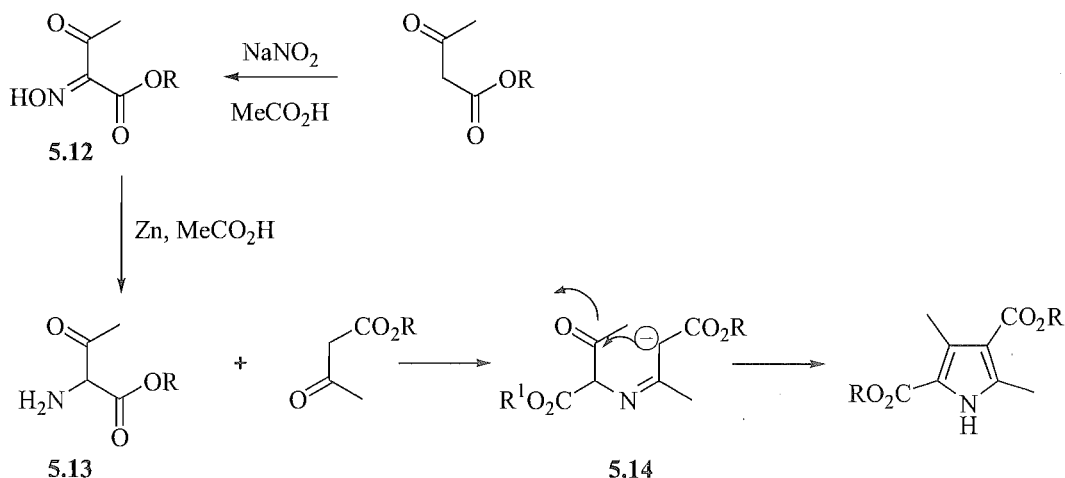
Due to their widespread applications in nature and science, considerable efforts have been devoted to the development of straightforward reactions to build up pyrroles. The simple

methods widely used in this context involve the cyclization reactions, e.g. the Paal-Knorr<sup>12</sup> synthesis, the Knorr<sup>13</sup> synthesis and the Hantzsch<sup>14</sup> synthesis. The Paal-Knorr synthesis involves the reaction of a 1,4-dicarbonyl compound with  $\text{NH}_3$ , primary amines, hydroxylamines or hydrazines. The cyclization is thought to occur by the nucleophilic attack on the carbonyl group probably through the intermediate **5.11**.



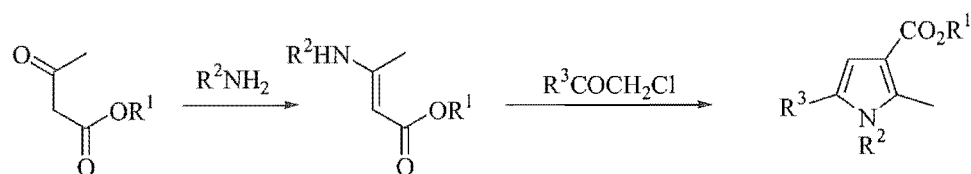
Scheme 5.1: The Paal-Knorr synthesis of Pyrroles.

The Knorr synthesis, an aldol-type cyclization, involving the attack by a nucleophilic carbon on the carbonyl group, provides route to a variety of pyrroles. The reaction uses two moles of the starting  $\beta$ -ketoester, one being nitrosated and reduced *in situ* to give an aminoketone **5.13** (via the intermediate oximinoketone **5.12**), which then reacts with the second mole to give the pyrrole via the intermediate **5.14** (Scheme 5.2).



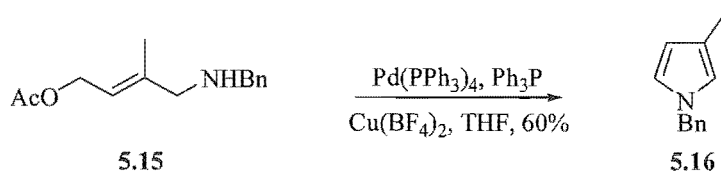
Scheme 5.2: The Knorr synthesis of Pyrroles.

The Hantzsch synthesis involves the reaction of an  $\alpha$ -haloketone with a  $\beta$ -ketoester and ammonia or a primary amine as depicted in Scheme 5.3.



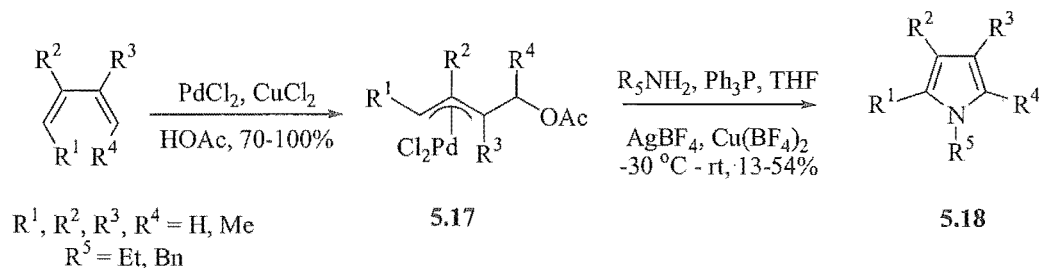
Scheme 5.3: The Hantzsch synthesis of Pyrroles.

Other methods involve metal-catalyzed cyclizations involving precursors that possess the requisite nitrogen nucleophile and an alkene in the same molecule. For example Bäckvall and co-workers<sup>15</sup> have synthesized a pyrrole **5.16** by a Pd-catalyzed cyclization of the amine **5.15**.



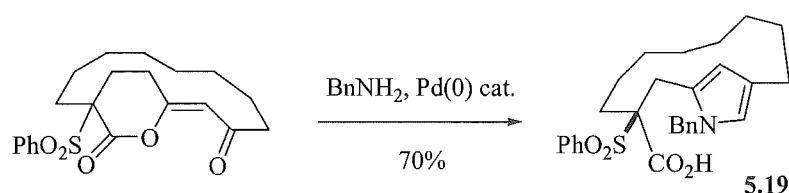
Scheme 5.4: Synthesis of Pyrrole **5.16**.

Bäckvall and co-workers<sup>16</sup> have found that primary amines react with the dienes via a  $\pi$ -allyl Pd intermediate **5.17** to give the pyrroles **5.18** in variable yields.



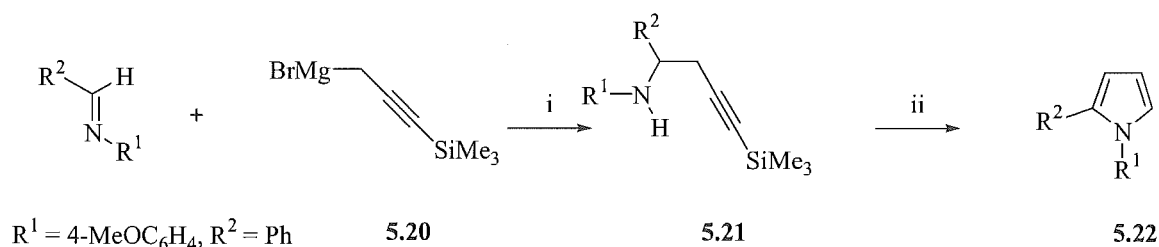
Scheme 5.5: Synthesis of Pyrroles **5.18** via  $\pi$ -allyl Pd intermediate **5.17**.

Fürstner *et al.*<sup>17</sup> have synthesized a pyrrole ring **5.19** via a Pd(0)-mediated reaction (Scheme 5.6) in the first total synthesis of roseophilin.



Scheme 5.6: Synthesis of Pyrrole **5.19** in the total synthesis of roseophilin.

Alkynes also serve as the recipients of cycloamination protocols. For example Knölker *et al.*<sup>18</sup> have carried out a Ag(I) promoted cycloamination of homopropargyl amine **5.21** (formed by the addition of an alkynyl Grignard reagent **5.20** to a Schiff base) to give 1,2-disubstituted pyrrole **5.22** as depicted in Scheme 5.7.

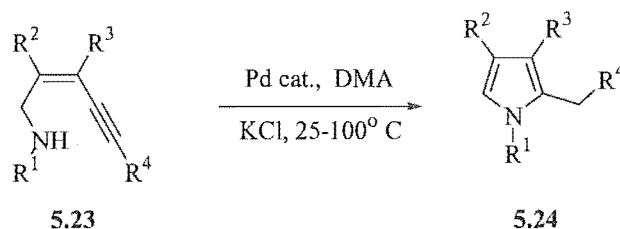


Reagents and conditions: i) a)  $\text{BF}_3\text{-Et}_2\text{O}$ , THF,  $-23^\circ\text{C}$ , 30 min; b)  $\text{Et}_2\text{O}$ ,  $-23^\circ\text{C}$ , 15h.  
ii) 1.1 eq.  $\text{AgOAc}$ , DCM, rt, 14h.

Scheme 5.7: Synthesis of Pyrroles **5.22** from **5.21**.

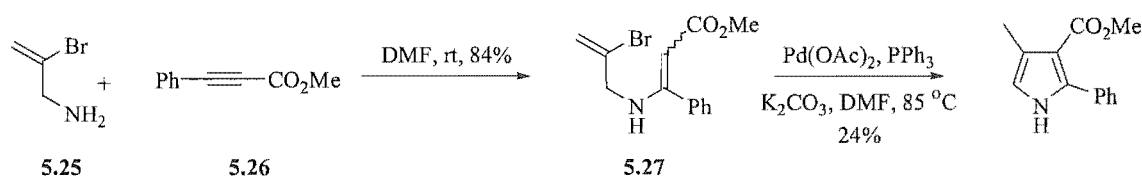
Gabriele *et al.*<sup>19</sup> reported a related cycloisomerization of (*Z*)-2-en-4-ynyl amines **5.23** to substituted pyrroles **5.24** in the presence of a Pd(II) catalyst and KCl in *N,N*-dimethylacetamide as shown in Scheme 5.8. Ring-closure occurs at rt if  $R^3$  is equal to H, otherwise heating is required for the cycloisomerization.





Scheme 5.8: Synthesis of Pyrroles 5.24 from 5.23.

Grigg *et al.*<sup>20</sup> carried out a palladium-catalyzed intramolecular cyclization of an enamine 5.27 containing a vinyl bromide (formed from an amine 5.25 and alkyne 5.26 or an allene) as illustrated in Scheme 5.9.



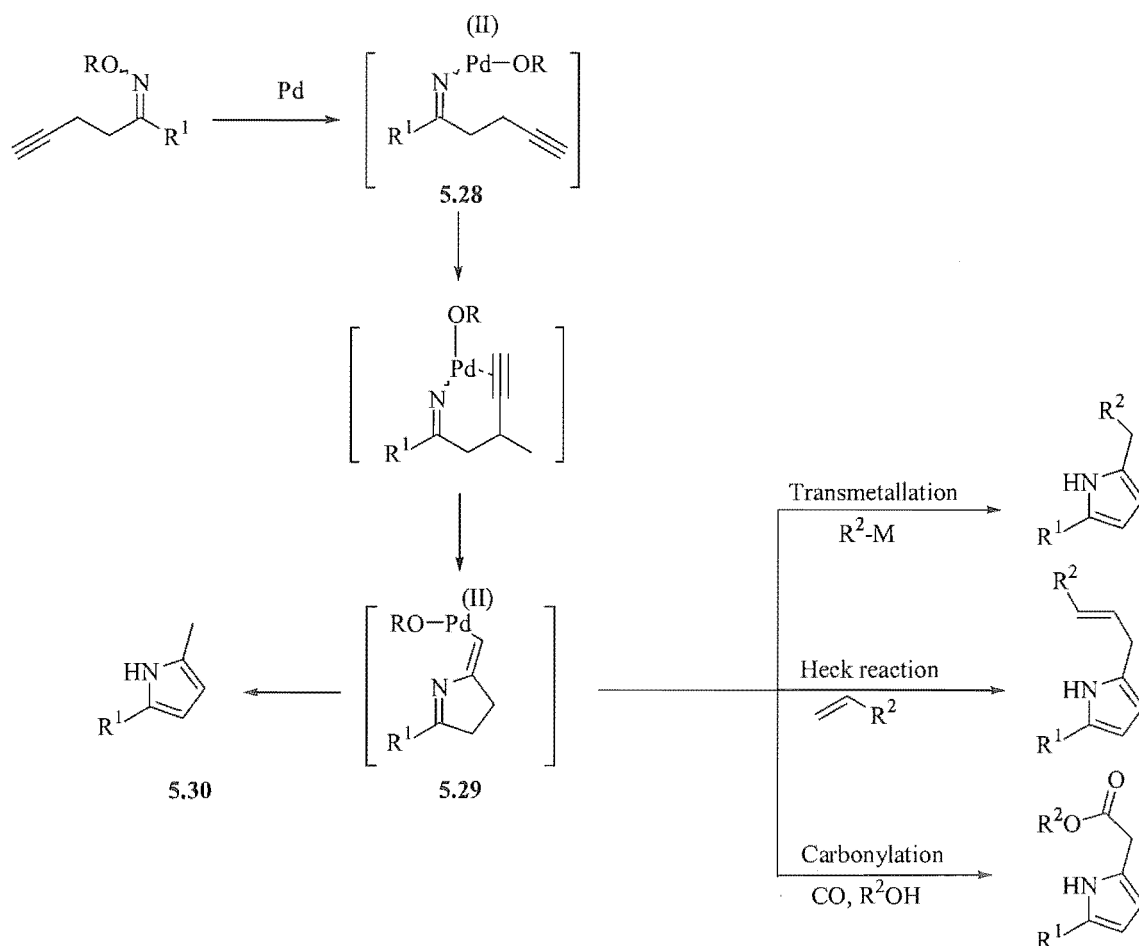
Scheme 5.9: Pd-catalyzed cyclization of 5.27.

Various substituted pyrroles have been synthesized by Narasaka *et al.*<sup>21</sup> via A-H cyclizations of olefinic oximes, as discussed earlier in chapter 2 (section 2.5, Table 2.1). Various applications of A-H reactions have been reported for the synthesis of different N-heterocycles from olefinic oximes. Here, I report the first A-H cyclization of alkynyl derivatives of *O*-pentafluorobenzoyl oximes followed by other domino processes, applied to the synthesis of 2,5-functionalized pyrroles. What follows is a discussion about the synthetic plan involved in the synthesis of pyrroles.

## 5.2. Synthetic Plan for the Synthesis of Pyrroles

The synthetic strategy involved in the synthesis of pyrroles was based on the A-H reaction of propargylic *O*-pentafluorobenzoyl derivatives of oximes as outlined in Scheme 5.10.

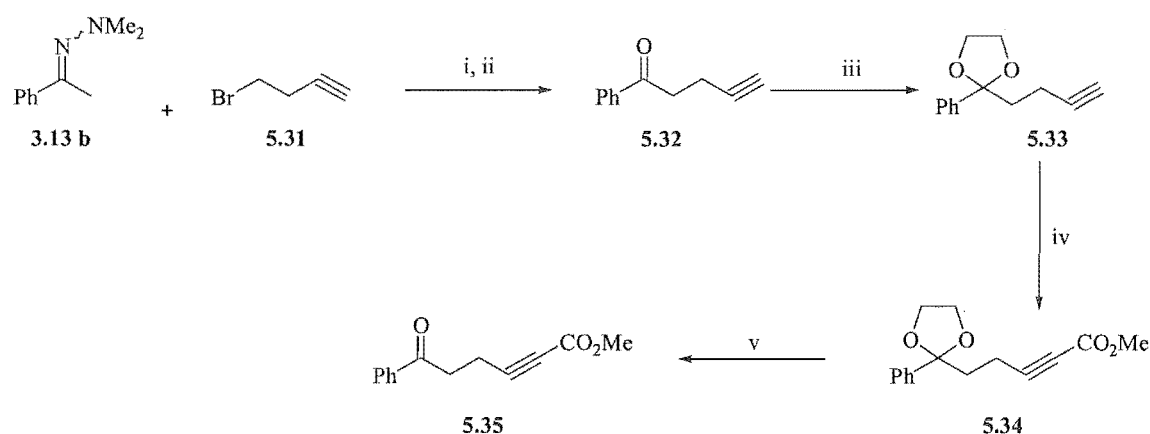
Oxidative addition of Pd(0) to the N-O bond of oxime would occur to give the alkylideneaminopalladium(II) complex **5.28** which would add to the triple bond to give a living alkenylpalladium(II) complex **5.29**. The termination of **5.29** is vital for the regeneration of the Pd catalyst to the catalytic cycle. This could be accomplished in a number of ways. For example, termination by dehydropalladation (under A-H reaction conditions) would give the pyrrole **5.30**, whereas termination by transmetalation with organometallic compounds, intermolecular Heck reaction or CO insertion followed by a nucleophile, would give rise to a variety of 2-substituted 5-functionalized pyrroles as depicted in Scheme 5.10.



Scheme 5.10: Synthetic plan for the synthesis of functionalized pyrroles.

### 5.3 Synthesis of substrates for the Preparation of Pyrroles

The synthesis of alkynyl ketones is outlined in Scheme 5.11. The aryl ketone containing terminal alkyne moiety was synthesized by alkylation of the *N,N*-dimethylhydrazone **3.13b** (derived from acetophenone) with 4-bromo-1-butyne **5.31** and successive hydrolysis.<sup>22</sup> The crude alkynyl ketone derivative was purified by flash column chromatography to give **5.32** in 91% as depicted in Scheme 5.11.



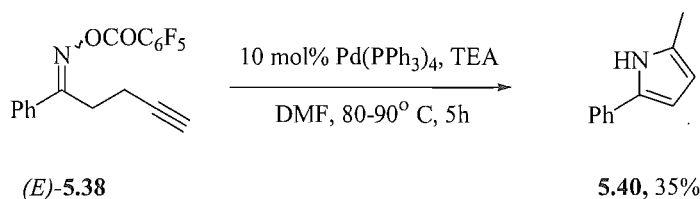
Reagents and conditions: i) LDA, THF, 1h; then propargyl bromide **5.31**,  $-78^{\circ}\text{C}$ -r.t., 16h. ii) NaOAc, AcOH, THF, water, rt, 3h. iii) ethylene glycol,  $\text{C}_6\text{H}_6$ , *p*-TsOH, reflux, 3h. iv)  $-78^{\circ}\text{C}$ , n-BuLi, 1h, then  $\text{ClCO}_2\text{Me}$ , 4h. v) 1N HCl, THF, reflux.

Scheme 5.11: Synthesis of propargyl ketones **5.32** and **5.35**.

The internal alkyne derivative **5.35** was prepared subsequently from **5.32** in two steps by first protecting its carbonyl group as a ketal<sup>23</sup> (**5.33**), and then reacting the ketal (**5.33**) with methylchloroformate to give **5.34**. The ketal functionality of **5.34** was subsequently hydrolyzed by refluxing it with 1N HCl (aq.) in THF to give the internal alkyne derivative **5.35** in 88% yield.



The initial study was carried out using the terminal alkyne derivative (*E*)-**5.38**, which was subjected to the A-H reaction conditions first, using 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 5 equivalents of TEA in DMF at 80° C as shown in scheme 5.13.

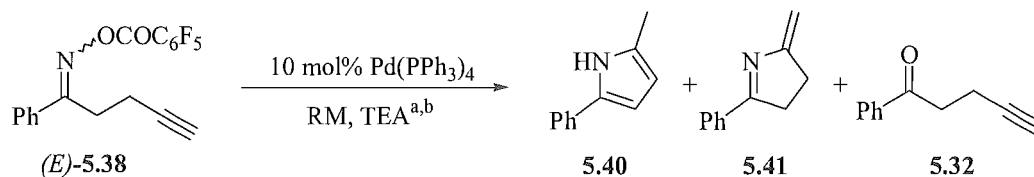


Scheme 5.13: Attempted synthesis of pyrrole **5.40** via A-H reaction of **5.38**.

The A-H reaction of (*E*)-**5.38** gave a complex mixture in 1h, which contained 35% of the pyrrole **5.40**. No further attempts were made to optimize the reaction conditions of A-H reaction of (*E*)-**5.38**.

Next the *O*-pentafluorobenzoyl oxime of the terminal alkyne derivative (*E*)-**5.38** was subjected to the A-H reaction conditions followed by transmetallation with different organometallics as summarized in Table 5.1. Attempts directed towards the termination of the living alkenylpalladium(II) complex (**5.29**, Scheme 5.10) by cross-coupling with PhSnBu<sub>3</sub> resulted in a complex mixture (entry 1), which contained only 7% of the pyrrole formed from the isomerisation of **5.29**. The reaction was not even successful by changing the reaction medium from DMF to THF (entry 2). The A-H reaction followed by transmetallation with PhZnBr was also attempted at rt in THF as depicted in Table 5.1. When PhZnBr was added in 20 minutes, no product of transmetallation was observed, but the dihydropyrrole **5.41** was obtained in 28% as well as 11% of the starting material and 16% of the corresponding ketone were formed (entry 3). The slow addition (in 2h) of PhZnBr did not allow the transmetallation to happen either (entry 4), and again the premature products was obtained as a mixture of the pyrrole **5.40** (9%) and the dihydropyrrole **5.41** (5%).

Table 5.1: The A-H reaction followed by transmetallation with different organometallic reagents.



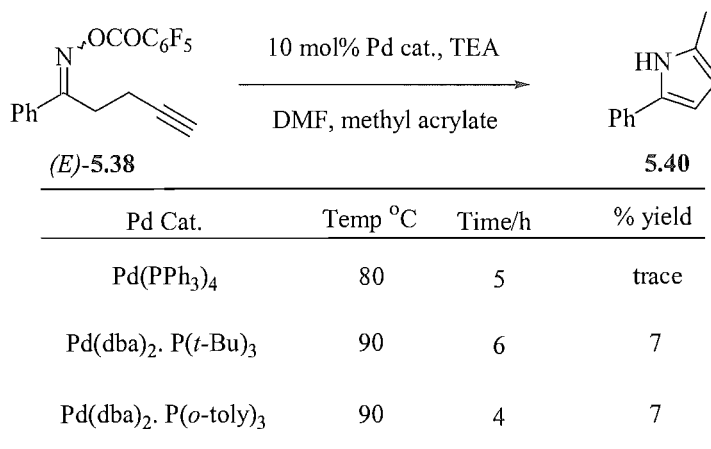
Entry	RM	solvent	temp/ °C	time/ h	Yield %			
					5.32	5.38	5.40	5.41
1	PhSnBu <sub>3</sub>	DMF	70	11	-	-	7	-
2	PhSnBu <sub>3</sub>	THF	70	11	-	-	12	-
3	PhZnBr <sup>a</sup>	THF	rt	3	16	11	-	28
4	PhZnBr <sup>b</sup>	THF	rt	3	-	5	9	5

a) PhZnBr added over 20 min. The reaction was carried out in the absence of TEA.

b) PhZnBr added over 2 h. The reaction was carried out in the absence of TEA.

The failure of transmetallation reaction and the isolation of the intermediate pyrrole and dihydropyrrole indicate that the intermediate alkenylpalladium(II) complex (**5.29**, Scheme 5.10) does not react further under the reactions tried during this work.

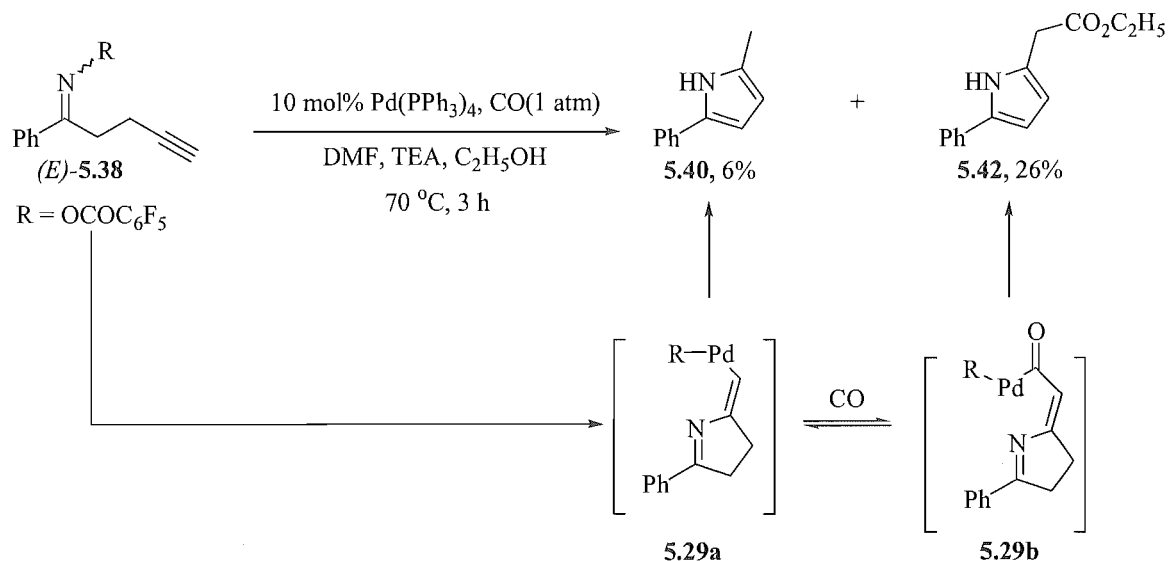
Attempts were next diverted to check the possibility of an intermolecular olefin insertion via Heck reaction into the alkenylpalladium(II) intermediate (**5.29**, Scheme 5.10). The A-H reaction of (*E*)-**5.38** followed by double bond insertion of methyl acrylate, was analysed using different Pd catalysts including Pd(PPh<sub>3</sub>)<sub>4</sub>, Pd(dba)<sub>2</sub>.P(*o*-tolyl)<sub>3</sub> and Pd(dba)<sub>2</sub>.P(*t*-Butyl)<sub>3</sub>. However, the alkenylpalladium (II) intermediate (**5.29**, Scheme 5.10) did not seem to react further, as very low yields of the pyrrole **5.40** were obtained as illustrated in Scheme 5.14.



Scheme 5.14: Attempted synthesis of functionalized pyrroles via A-H reaction followed by sequential olefin insertion.

The results were not so promising using the transmetallation and intermolecular Heck reaction for termination of the living Pd complex. In each case, the premature product, i.e. pyrrole was formed in very low yield and subsequent transmetallation and Heck reactions did not occur.

Finally, the insertion of CO into the alkenylpalladium(II) intermediate (**5.29**, Scheme 5.10), and termination by the addition of an alcohol, were undertaken as shown in Scheme 5.15. This domino process is thought to occur by the transformation of the alkenylpalladium(II) intermediate (**5.29a**) into an acylpalladium(II) complex (**5.29b**) by the reversible insertion of CO, followed by termination with ethanol. The domino A-H-carbonylation-termination by alcohol sequence of (*E*)-**5.38** resulted in the formation of the esterified product **5.42** in 26% yield, as well as the pyrrole **5.40** (6%) obtained by the dehydropalladation of **5.29a** (Scheme 5.15). The formation of the by product pyrrole **5.40** suggests that termination by intermediate **5.29a** by dehydropalladation competes with the acyl palladium intermediate **5.29b**, and sequential termination by C<sub>2</sub>H<sub>5</sub>OH. The formation of the pyrrole **5.40** could probably be suppressed by carrying out the reaction under a high pressure of CO, however, no such attempts were made during the course of this study.

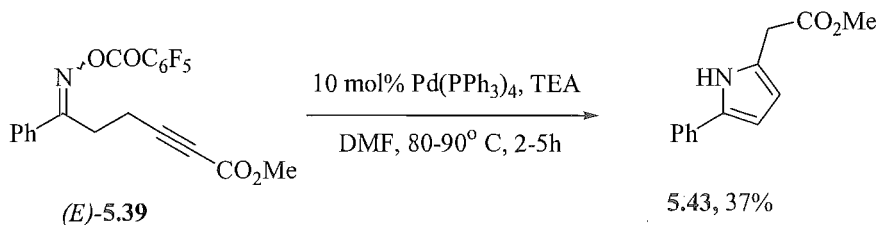


Scheme 5.15: A-H reaction of **5.38** followed by sequential insertion of CO and  $\text{C}_2\text{H}_5\text{OH}$ .

The reason for the success of the carbonylation reaction could be the fast insertion of CO into the alkylideneamino Pd complex, compared to transmetallation and Heck reaction.

#### 5.4.2 Cyclization of the Internal Alkyne Derivative<sup>24</sup>

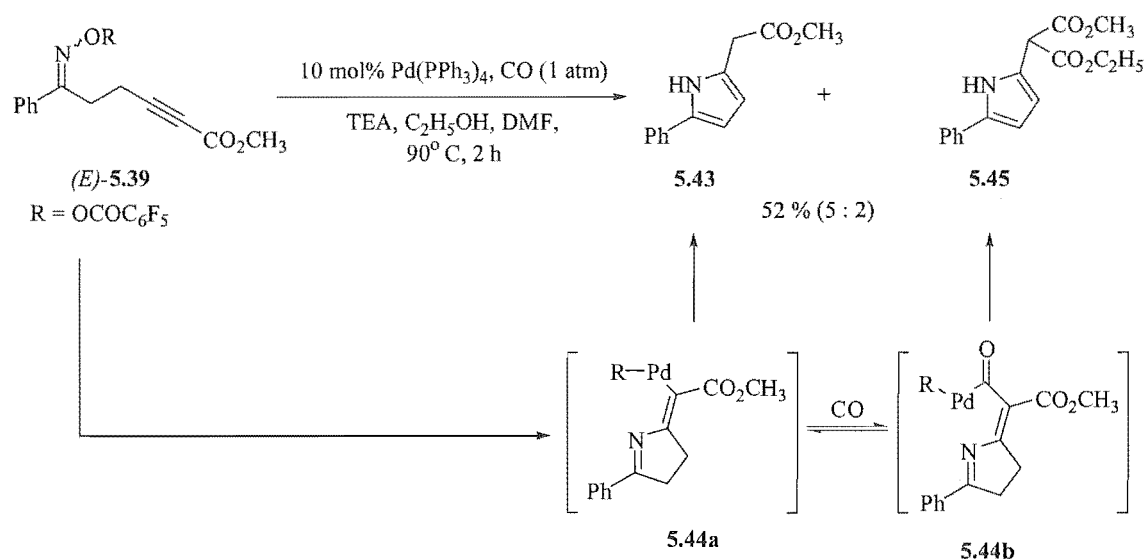
Next, the A-H reaction of the internal alkyne based *O*-pentafluorobenzoyl oxime (*E*)-**5.39** was carried out using 10 mol%  $\text{Pd}(\text{PPh}_3)_4$ , 5 eq. of TEA in DMF at  $80^\circ\text{C}$  in 2h to give a 37% of the cyclised pyrrole **5.43** as depicted in Scheme 5.16.



Scheme 5.16: Synthesis of functionalized pyrroles via A-H reaction .



The domino A-H-carbonylation-termination (via alcohol) of (*E*)-**5.39** resulted in 52% of a mixture of the esterified product **5.45** formed from the acylpalladium complex **5.44b** and the premature product **5.43** formed from dehydropalladation of the alkenylpalladium(II) complex **5.44a** (Scheme 5.17).



Scheme 5.17: Synthesis of functionalized pyrroles via A-H reaction followed by carbonylation and tandem insertion of alcohol.

The formation of a mixture of the esterified product **5.45** and the pyrrole **5.43** reflect again (as for the terminal alkyne derivative **5.38**) the competition between the complex **5.44a** and the acylpalladium complex **5.44b**.

In summary, various efforts were made for termination of the living alkenylpalladium complexes via different approaches including transmetallation, intermolecular Heck reaction, and carbonylation followed by termination with alcohols. The results from transmetallation and intermolecular Heck reaction were disappointing, however, comparatively better results were obtained by using carbonylation-termination via alcohols

sequence, which indicate that an array of 2,5-disubstituted pyrroles could be synthesized using this methodology.

## 5.5 Conclusion and Future Work

The A-H reaction of propargyl derivatives of *O*-pentafluorobenzoyl oximes has been investigated. The A-H reaction of both terminal and internal alkyne derivatives results in the synthesis of the corresponding pyrrole in moderate yield. Of the various domino processes coupled with A-H reaction, for the termination of the living Pd complexes, the carbonylation-termination by alcohols has been comparatively successful, and provide a convenient and new approach for the synthesis of 2-aryl pyrrole 5-methyl esters. However, this methodology needs further development.

Future work could include conducting the carbonylation reaction under high pressure of CO to minimize the premature termination of the alkenyl palladium complexes, and to improve the efficiency of the acylpalladium complexes to give the respective pyrrole-5-substituted methyl esters. Optimization of the reaction condition could also be accomplished to give better yields of the simple cyclised products via A-H cyclization. Attempts could also be made for the investigation of the yne-ene type cyclization using A-H reaction. Acceleration of the pyrrole synthesis using microwave irradiation could also be attempted.

Further work could also involve termination of the alkenyl palladium complexes using other domino processes including termination by N, O, other heteroatom nucleophiles, hydrogenolysis and C or O enolates.<sup>24</sup>

## 5.6 References for Chapter 5

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## **CHAPTER SIX**

### **RING CLOSING METATHESIS AS A GENERAL METHOD FOR THE SYNTHESIS OF AZA- HETEROCYCLES**

## 6.1 Introduction

The olefin metathesis reaction has gathered a widespread interest as a powerful tool in synthetic organic chemistry (see Chapter 1). Ring closing metathesis, a type of olefin metathesis has been used extensively to form functionalized heterocyclic rings present in natural products and other biologically active compounds.<sup>1,2</sup> It has also found elegant applications in total syntheses. Here, a detailed discussion about the catalysts, mechanism and applications of ring closing metathesis methodology involved in the synthesis of heterocycles is presented.

Olefin metathesis is a powerful carbon-carbon bond forming reaction that redistributes unsaturated functionalities between substrates, was first reported<sup>3</sup> in 1955; its origin can be traced to the development of Zeigler polymerization reactions. The reaction involves bringing together two olefins to form a new double bond (Figure 6.1), in the presence of a transition metal catalyst. The generality of this reaction has been largely underpinned by the development of well-defined transition metal alkylidene complexes, as well as the convenient operation of the reaction at rt or near rt, in a variety of media (aqueous or organic). The main types of olefin metathesis are summarized in Figure 6.1.

Ring closing metathesis, a subtype of olefin metathesis, has the ability to transform an acyclic diene into an olefinic ring. Although, RCM has been widely used in industry for the production of linear olefins and polymers,<sup>4</sup> it has only relatively recently been used extensively by organic chemists in the synthesis of numerous carbocycles and heterocycles.

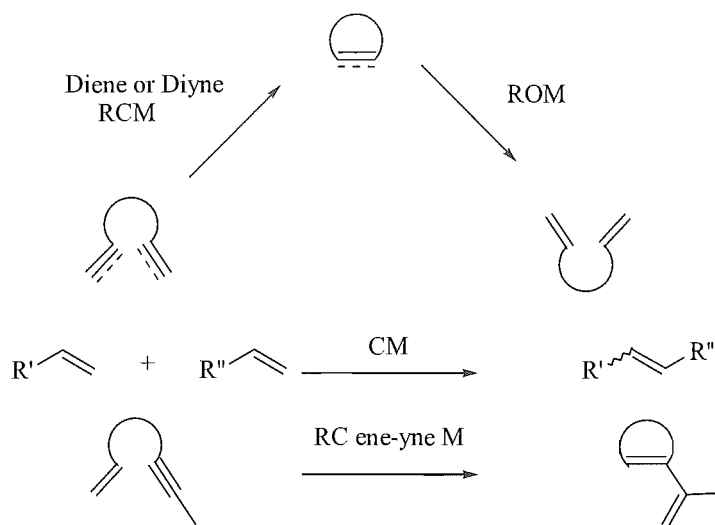
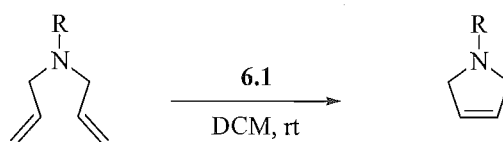


Figure 6.1: General types of Olefin metathesis reactions

The use of ring-closing metathesis to form nitrogen heterocycles was first reported by Grubbs<sup>5</sup> and Fu in 1992, who explored the cyclization of N-substituted dienes to dihydropyrroles in the presence of molybdenum carbene catalyst **6.1** developed by Schrock<sup>6</sup> and co-workers (Scheme 6.1).



R = COCF<sub>3</sub>, Boc, Bn, HCl.

Scheme 6.1: Synthesis of dihydropyrroles by RCM.

The mechanism of ring closing metathesis is depicted in Figure 1.6 (chapter 1). What follows is a discussion about the catalysts development and functionality tolerance of these catalysts involved in ring closing metathesis.

## 6.2 Catalysts development and functional group tolerance

The generalization of RCM is directly correlated to the breakthrough in the development of metal-carbene catalysts, especially by Schrock<sup>6</sup> and Grubbs.<sup>7</sup> The studies by these two groups have led to the functional group tolerant ruthenium and molybdenum catalysts that can affect the cyclization of a diverse range of substrates under milder reaction conditions leading to the synthesis of a variety of heterocyclic and carbocyclic rings. These include molybdenum-based complex **6.1**, developed by Schrock and co-workers,<sup>6</sup> and the ruthenium-based complexes **6.2** and **6.3** developed by Grubbs and co-workers<sup>7</sup> (Figure 6.2). The ruthenium-based catalyst **6.2** is less air and moisture-sensitive compared to the molybdenum-based catalyst **6.1**, easy in handling, and thus most commonly used. Catalysts **6.1-6.3** have the capability of catalyzing the formation of simple 5-7 membered mono and bicyclic rings. Although the catalyst **6.1** is more air and moisture sensitive compared to **6.2** and **6.3**, it is more active than **6.2-3**, that it can catalyze the formation of tri- and tetra-substituted alkenes, which is otherwise very slow or impossible with catalysts **6.2** or **6.3**.<sup>8</sup> However, catalyst **6.3** with extended carbene tether is known to catalyze the RCM of more hindered substrates by exhibiting an increased coordination during the formation of intermediate metallocyclobutanes.<sup>9,10</sup> After the introduction of Schrock's catalyst **6.1**, and Grubbs' first generation catalysts **6.2** and **6.3**, numerous other catalysts have been developed with improved reactivity and selectivity. Some of the commonly used catalysts in RCM are summarized in Figure 6.2.



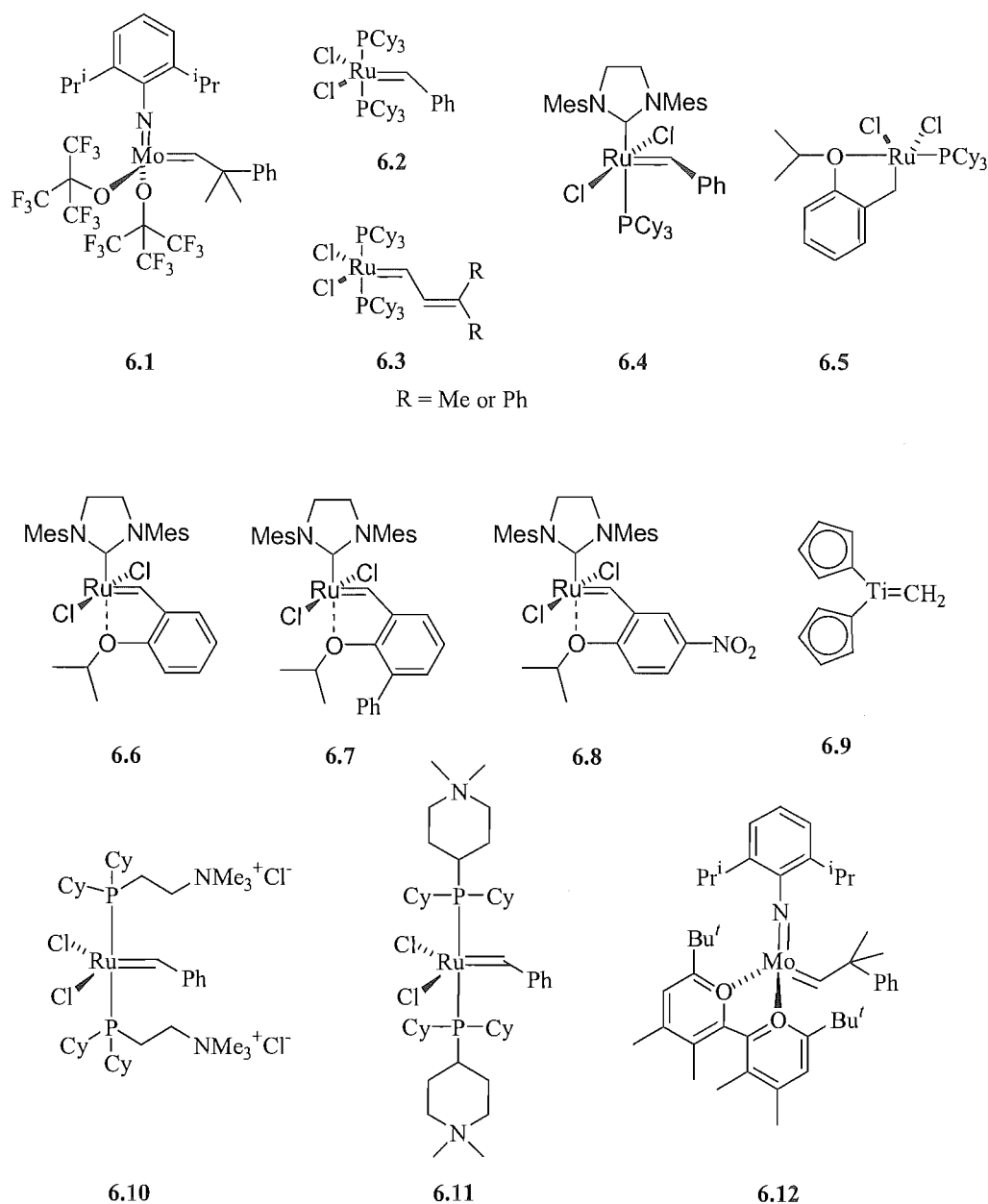


Figure 6.2: Catalysts used for olefin metathesis

Subsequent exchange of a  $\text{PCy}_3$  group of **6.2** with *N*-heterocyclic carbene led to the ‘second-generation’ metathesis catalysts with improved reactivity, selectivity and

stability.<sup>11-13</sup> The reactivity of catalysts **6.4**, and its analogues is thousand times superior compared to first generation catalyst **6.2**, and efficiently catalyze ring closing metathesis reactions of substrates that were previously inactive to **6.2**. Hoveyda and co-workers have developed robust ruthenium-based carbenes containing internal oxygen chelates, **6.5**<sup>14</sup> and **6.6**,<sup>15</sup> which are stable to silica gel chromatography and can be recycled without any detectable loss of reactivity. Hoveyda catalyst **6.6** (Figure 6.2), offers better reactivity than **6.4** towards electron-deficient olefins. Wakamatsu and co-workers further modified catalysts **6.6** by the replacement of isopropoxybenzylidene ligand with biphenyl-based benzylidene<sup>16</sup> (**6.7**, see Figure 6.2) or with BINOL<sup>17</sup> resulting in an improved reactivity of **6.7** than **6.6** and **6.4**. The replacement of the isopropoxybenzylidene group of catalyst **6.6** with nitrophenyl based benzylidene by Gerala *et al.*, resulted in the formation of catalyst **6.8**; exhibiting the same stability, and better reactivity than **6.6**.<sup>18</sup> This increase in reactivity could be attributed to the reduced electron density on the oxygen atom of **6.8**, due to the introduction of an electron-withdrawing NO<sub>2</sub> group, thus enhancing its catalytic activity. In addition, the titanium-based carbenes (e.g, **6.9**) have found only occasional use in RCM, and are widely used as olefination catalysts.<sup>19</sup> Grubbs and co-workers have also synthesized catalysts **6.10** and **6.11** that allow ring-closing metathesis in water and methanol.<sup>20</sup> The enhanced solubility and reactivity of catalysts **6.10** and **6.11** could be attributed to the quaternary ammonium phosphine ligands.

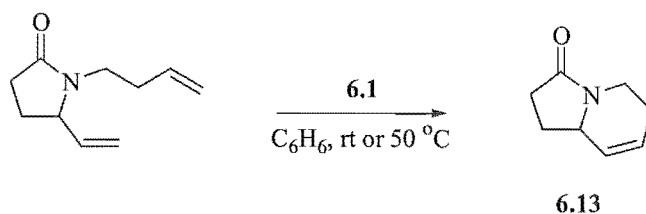
A significant advantage of these catalysts is their tolerance to a variety of functional groups. These catalysts have been used to cyclise compounds containing free alcohols, carbonyl groups and other potentially reactive functionalities. Such reactive functionalities are often not compatible with conventional methods of ring closure and usually require extensive protection.

### 6.3 Applications of RCM to the Synthesis of N-Heterocycles

Three major categories that can be identified based on the types of olefins directly involved in the RCM process are diene, enyne, and diyne metathesis. Among these subclasses, diene RCM has drawn significantly more attention from synthetic chemists due to its effectiveness in the formation of a range of cyclic structures, central to the synthesis of carbocycles, heterocycles, alkaloids and peptidomimetics, and has been well studied and reviewed.<sup>1,2,10</sup> What follows is a stepwise discussion of the applications of RCM to the synthesis of different N-containing heterocycles from diene, enyne (ene-yne-ene), and diyne precursors.

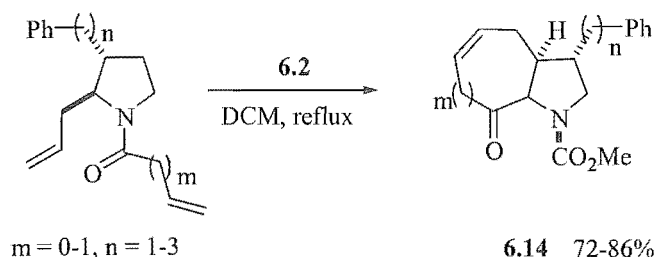
#### 6.3.1 RCM from Diene Precursors

After early reports by Grubbs and Fu<sup>5</sup> using RCM for the synthesis of dihydropyrroles, Martin *et al.* demonstrated its application in the presence of Schrock's catalyst **6.1** to the synthesis of fused aza-heterocycles (**6.13**) found in a number of alkaloids (Scheme 6.2).<sup>21</sup>



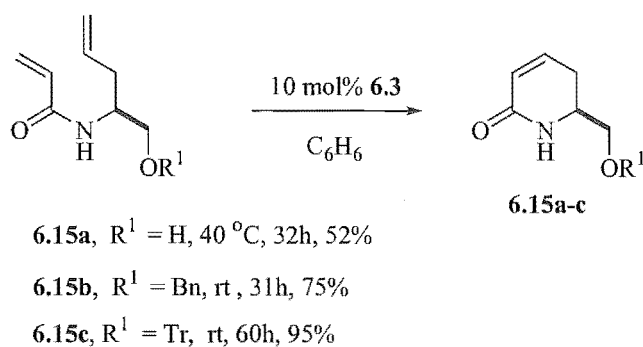
Scheme 6.2: Synthesis of dihydropyrroles **6.13** by RCM.

A number of other reports after Martin's work was published that lead to the synthesis of fused bicyclic lactams.<sup>22</sup> Recently, Hanessian *et al.* have reported the synthesis of a range of bicyclic fused indolizidinones (**6.14**), which have found applications as constrained mimetics of peptide  $\beta$ -turns, by RCM in the presence of Grubbs' catalyst **6.2** in 72-86% yields (Scheme 6.3).<sup>23</sup>



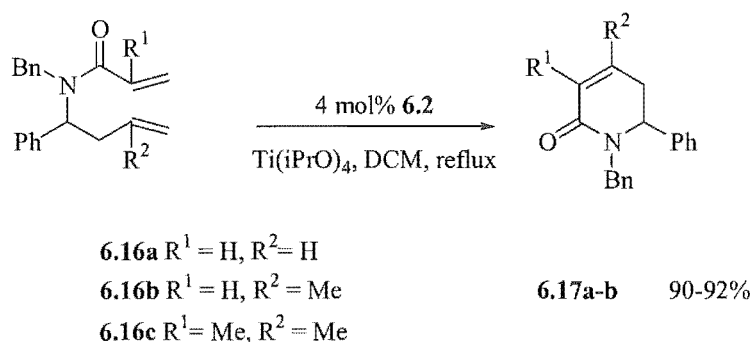
Scheme 6.3: Synthesis of fused bicyclic lactams by RCM.

In addition to fused bicyclic lactams, there are numerous applications of RCM for the synthesis of medium<sup>24</sup> to large size lactam rings. Huwe *et al.*<sup>25</sup> reported the synthesis of 6 membered lactam rings (**6.15a-c**) using extended chain catalyst **6.3**. The key observation of Huwe's work was that increased steric crowding around the oxygen substituent led to an increase in yield of the cyclised lactam. (See Scheme 6.4)

Scheme 6.4: Synthesis of lactams **6.15a-c** by RCM.

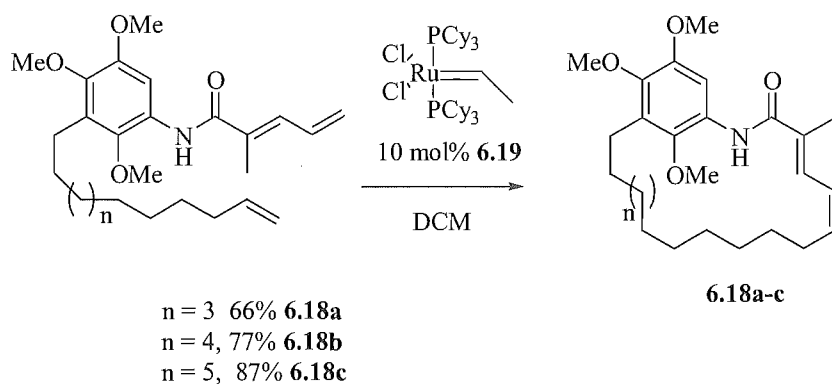
Rodríguez and co-workers<sup>26</sup> reported the successful ring closure of di- and tri-substituted olefins **6.16a-b**, to give six-membered  $\delta$ -lactams **6.17a-b**, in the presence of an additive  $\text{Ti}(\text{O}i\text{Pr})_4$  and the catalyst **6.2** (Scheme 6.5), which was previously reported to be unsuccessful in the RCM of tri-substituted dienes (in the synthesis of lactones).<sup>27</sup> However, the ring closure of the tetra-substituted diene derivative **6.16c** ( $R^1, R^2 = \text{Me}$ ) could not be achieved with either catalyst **6.2** or **6.4** (which has been reported to catalyze the RCM of

even tetra-substituted olefins),<sup>28</sup> in the presence or absence of  $\text{Ti}(\text{OiPr})_4$ , confirming that an increased degree of substitution on  $\text{C}=\text{C}$ ,<sup>26</sup> and in its close proximity<sup>29</sup> leads to blockage of the catalytic cycle.



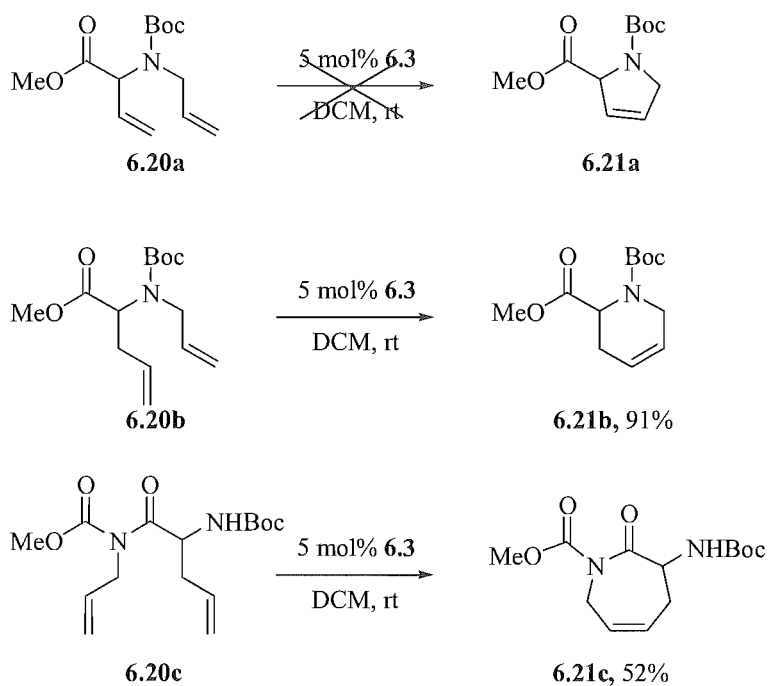
Scheme 6.5: Synthesis of conjugated six-membered lactams **6.17a-b** by RCM.

Ring-closing metathesis has also been successfully used for the synthesis of macrocyclic lactams. Lemarchand *et al.*<sup>30</sup> have recently reported the synthesis of 16-20 membered *para*-quinone macrolactams **6.18**, related to antitumor agent geldanamycin, using RCM in the presence of 10 mol% of an ethylidene ligand catalyst **6.19** [(prepared by the replacement of benzylidene ligand of **6.2** by an ethylidene ligand), (Scheme 6.6)]. They found that the 18-20 membered macrolactams were readily accessible using RCM, however, 16-17 membered rings could not be synthesized.



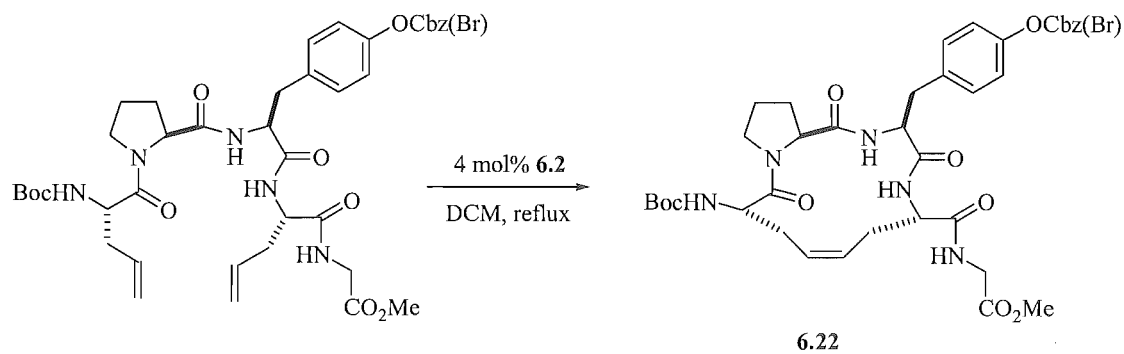
Scheme 6.6: Synthesis of macrolactams **6.18a-c** by RCM.

Ring-closing metathesis has found applications in the synthesis of rigidified peptides. Initial results by Miller and co-workers<sup>31</sup> involved the synthesis of 5-7-membered  $\alpha$ -amino  $\epsilon$ -lactams **6.21a-c** from olefinic linkers **6.20a-c** to constrain the peptide backbone in the presence of the extended chain catalyst **6.3** (see Scheme 6.7). Ring closure of diene linker **6.20a** could not be achieved, whereas, six and seven-membered rings were formed in 91 and 52% yields respectively (Scheme 6.7).

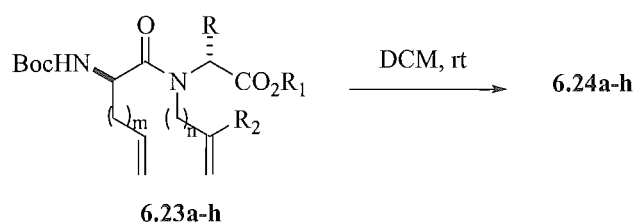


Scheme 6.7: Synthesis of constrained peptidomimetics using RCM.

The same report<sup>31</sup> also included the synthesis of  $\beta$ -turn mimetic **6.22** using catalyst **6.2** in 80% yield (Scheme 6.8).

Scheme 6.8: Synthesis of macrolactam **6.22** using RCM.

The scope of RCM has also been extended to the synthesis of  $\alpha$ -amino acid derived Freidinger lactams (See Scheme 6.9).<sup>32</sup> RCM of vinyl glycine-based linker **6.23a** was achieved in refluxing DCE to give **6.24a** in 53% yield after 48h in the presence of catalyst **6.2**. *N*-Allyl glycine derived diene linkers **6.23b-c** cyclized smoothly to give the corresponding seven-membered lactams **6.24b-c** in 68 and 42% yields respectively, in the presence of 10 mol% catalyst **6.2**. The methyl-substituted diene linker **6.23d** cyclized in the presence of the catalyst **6.4** to give the 89% of azepinone.



<b>6.24</b>	<b>a</b>	<b>b</b>	<b>c</b>	<b>d</b>	<b>e</b>	<b>f</b>	<b>g</b>	<b>h</b>
R	H	H	Me	H	H	Me	H	H
R <sub>1</sub>	Et	Et	Me	Et	Et	Me	Et	Et
R <sub>2</sub>	H	H	H	Me	H	H	H	H
m	0	1	1	0	1	1	1	1
n	1	1	1	1	2	2	3	4
yield	53	68	42	89	70	60	86	8

Reagents and conditions: 10 mol% **6.2** or 5 mol% **6.4**, DCM, rt.

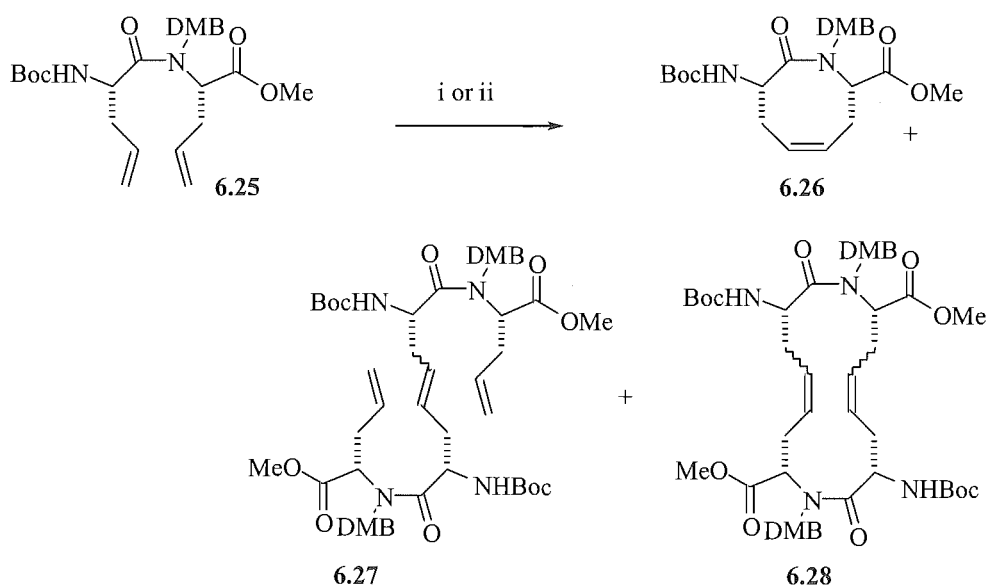
Scheme 6.9: Synthesis of 6-10 membered Freidinger lactams **6.24a-h** by RCM.

The synthesis of 8-membered rings by RCM (at a higher concentration) is a well-known challenge, and usually oligomerization of the starting diene occurs after sometime.<sup>33</sup> The cyclization of the diene linker **6.23e** was carried out at a lower concentration of 2 mM to avoid any oligomerization. Thus, the azocanone **6.24e** was isolated in 70%, without the formation of any byproducts. The alanine-based diene **6.23f** cyclised to give the azocanone



**6.24f** in moderate yield (60%). The reaction worked well for the synthesis of only *cis* isomer of 9-membered azacycle **6.24g** (86%). The 10-membered azacycle **6.24h** was synthesized using catalyst **6.4** in 8% isolated yield at a further lower concentration of 0.5 mM.

Creighton *et al.* have studied the synthesis of constrained eight-membered cyclic peptidomimetics using Grubbs' catalysts **6.2** and **6.4** (Scheme 6.10).<sup>33</sup> They found that the diene linker **6.25** cyclised smoothly in the presence of catalyst **6.2** at a lower concentration of 3 mM to give **6.26** in excellent yield (80%). However, RCM at a higher concentration (12, 50, and 100mM) led to the formation of byproducts **6.27** and **6.28** from the oligomerization of **6.25** and **6.26**.



Reagents and conditions: i) **6.25** (3 mM), **6.2**, DCM, reflux, 48-72h, 80%.  
 ii) **6.25** (12, 50 and 100 mM), **6.2** or **6.4**, DCM, reflux, 48-72h.

Scheme 6.10: Synthesis of **6.26**, **6.27** and **6.28** from acyclic diene **6.25**.

Further applications of RCM include the synthesis of P and S tethered analogues **6.30**<sup>34</sup> and **6.31**<sup>35</sup> of cyclic ureas<sup>†</sup> (e.g. **6.29**), a class of compounds known to be potent inhibitors of HIV (Figure 6.3).

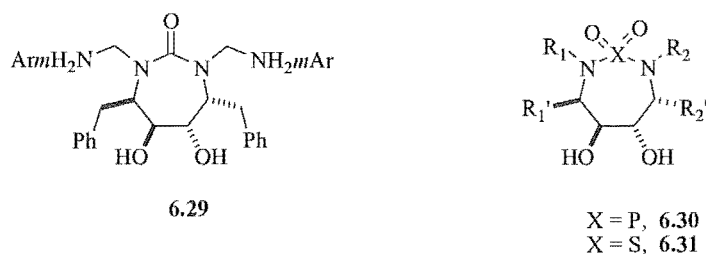
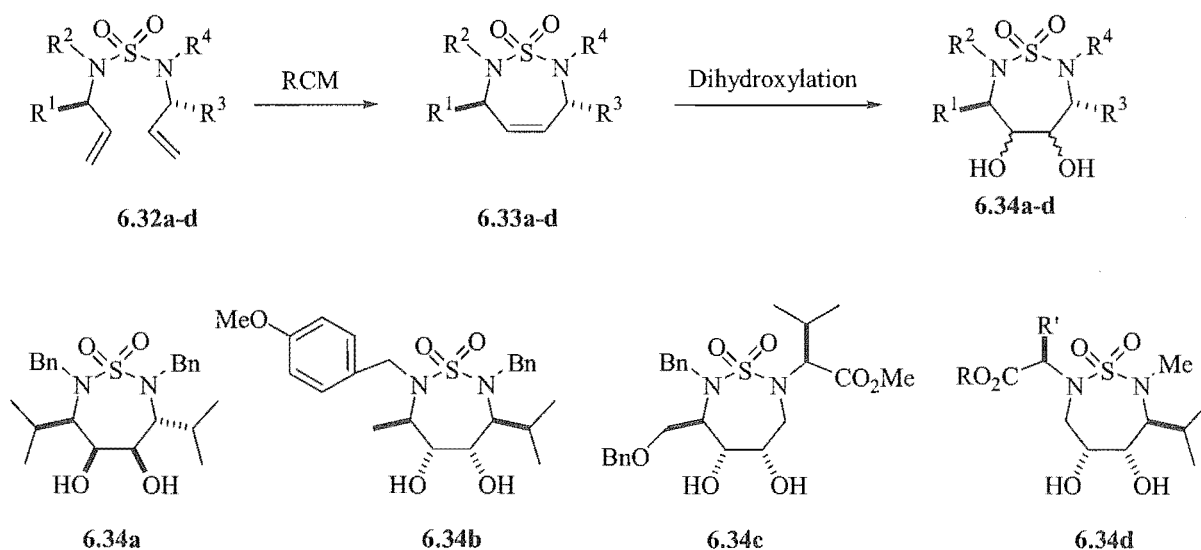


Figure 6.3: Cyclic urea **6.29** and its analogue **6.30** & **6.31**.

The ring closing metathesis of dienes **6.32a-d** gave heterocyclic compounds **6.33a-d**, which were subjected to dihydroxylation in the presence of OsO<sub>4</sub> and NMO to give HIV protease inhibitors (cyclic urea analogues) **6.34a-d** (Scheme 6.11).



Scheme 6.11: RCM of dienes **6.32a-d** to **6.33a-d**.

<sup>†</sup> A more detailed discussion about cyclic ureas is presented in chapter 7.

One major drawback of the synthesis of macrocyclic alkenes formed by RCM of diene precursors is the lack of control over the stereochemistry of the new double bond, with mixtures of (*E*)- and (*Z*)-isomers being formed. This is exemplified, by several approaches to epothilone A: although different research groups succeeded in the synthesis of 16-membered ring of this promising chemotherapeutic agent by RCM,<sup>36</sup> (*E,Z*)-mixtures of isomers are formed affecting the yield of the target molecule, as only the (*Z*)-alkene can be converted into the target. The fact that the required (*Z*)-isomer was formed as the minor product in many cases attests to the relevance of this stereochemical issue. This issue is solved by the RCM of diyne precursors, which will be discussed in section 6.2.3. What follows is a discussion about the ring closing ene-yne metathesis and ring closing ene-yne-ene metathesis.

### 6.3.2 RCM from ene-yne or ene-yne-ene Precursors

Despite its enormous potential, ring closing ene-yne and ene-yne-ene metathesis is relatively underdeveloped compared to the diene RCM metathesis process.<sup>37</sup> The RCEYM is a powerful atom-economical<sup>38</sup> method to generate ring structures (e.g. bridged, multiply fused, and dumbbell-shaped ring systems) from molecules with tethered alkene and alkynes via a tandem ring closure. The significant potential of RCEYM in cyclic systems is somewhat compromised because of the *exo/endo*-mode selectivity problems. This *exo/endo*-mode selectivity also dictates the ring-size, such that the *endo*-mode ring closure have one more C than that derived from an *exo*-mode ring-closure.<sup>39</sup> It is known that the ring closing ene-yne metathesis usually follows the *exo*-mode path in the synthesis of small-medium sized rings,<sup>40</sup> whereas the macrocycles follow the *endo*-mode pathway.<sup>39</sup>

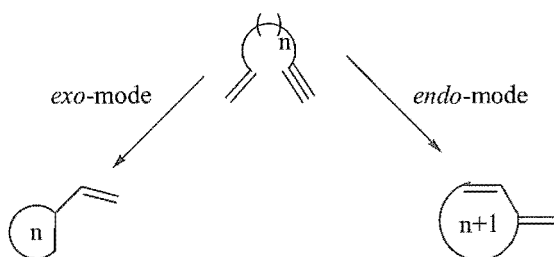
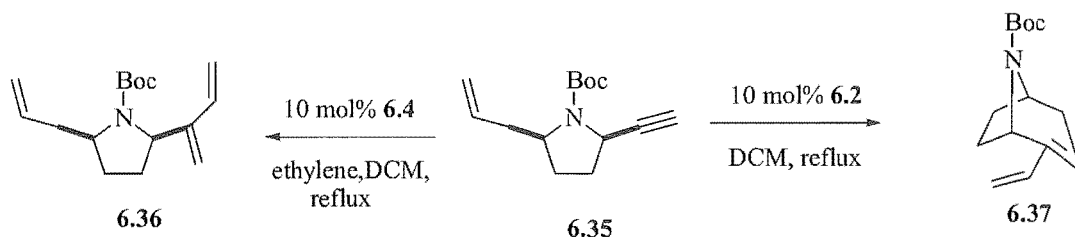
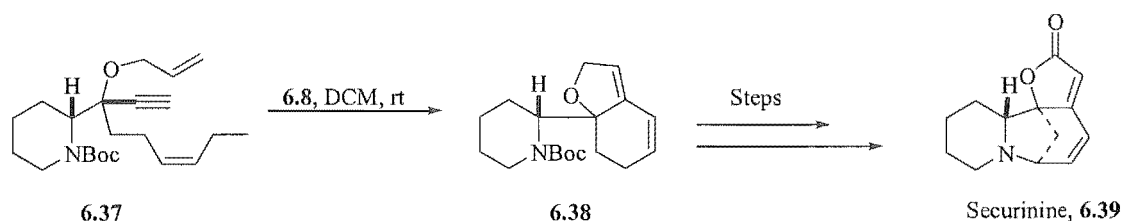


Figure 6.4: Mode selectivity in RCEYM.

Ring closing ene-yne metathesis of **6.35** in the presence of the active catalyst **6.4** under ethylene atmosphere gave the triene **6.36** as the major product (usually RCEYM reactions are carried out under ethylene atmosphere).<sup>41</sup> However, the same reaction in the presence of less active catalyst **6.2** under an inert atmosphere resulted in the synthesis of the tropane **6.37** as the sole product (Scheme 6.12).

Scheme 6.12: Synthesis of Tropane **6.37** by RCEYM.

RCEYEM has also been used as a key step in natural product synthesis. For example, the RCEYEM of substrate **6.37** in the presence of the highly active catalyst **6.8** (see Figure 6.2), gives the key intermediate **6.38** in the total synthesis of securinine **6.39** (Scheme 6.13).<sup>42</sup>

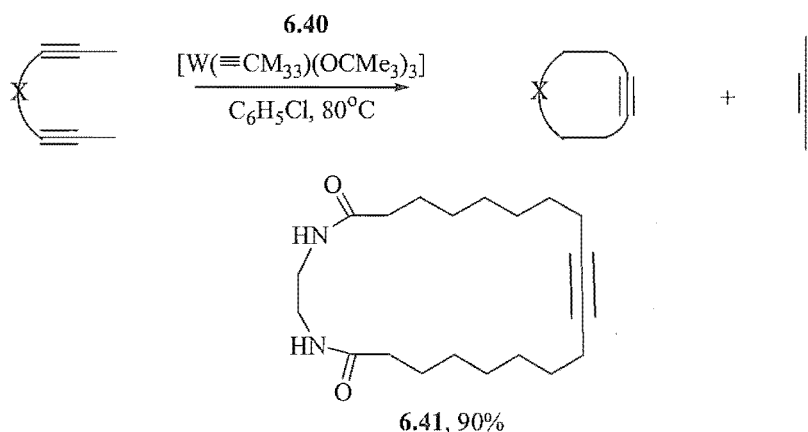


Scheme 6.13: RCEYEM of **6.37** to the key intermediate **6.38** in the total synthesis of securinine **6.39**.

In addition, ring closing ene-yne and ring closing ene-yne-ene metathesis have also successfully been applied to the synthesis of chiral ynamides and allenamides.<sup>43</sup>

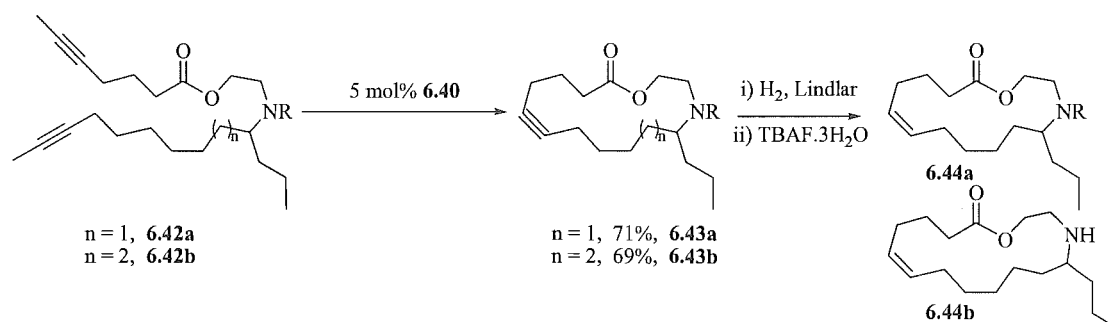
### 6.3.3 RCM from diyne Precursors

Unlike alkene metathesis, little attention has been paid to alkyne metathesis. Fürstner and co-workers<sup>45</sup> reported the first efficient synthesis of functionalized macrocycles [lactams (e.g. **6.41**), lactones and silyl ethers)] by the RCM of diyne substrates in the presence of tungsten catalyst **6.40** developed by Schrock,<sup>46</sup> in chlorobenzene or trichlorobenzene under high dilution conditions (Scheme 6.14). Fürstner *et al.* have described the suitability of only terminally substituted alkynes for the ring closing reaction (as the terminal alkynes are found to be incompatible<sup>46</sup> with catalyst **6.40**).



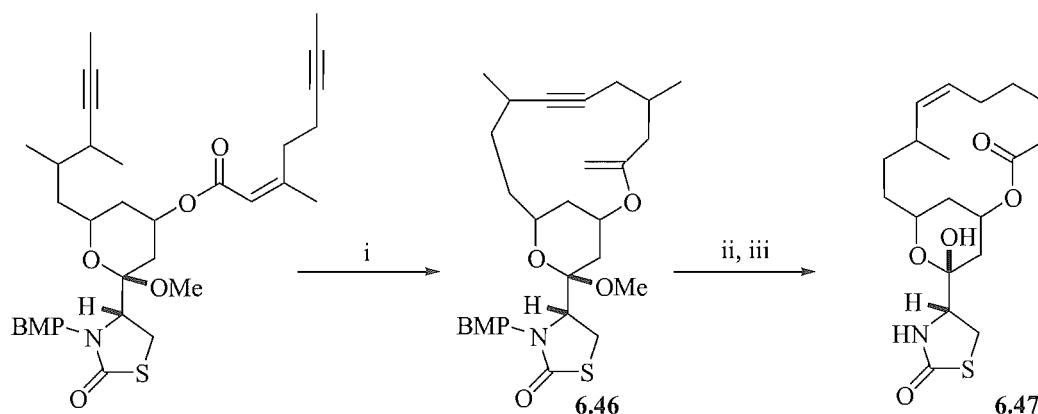
Scheme 6.14: Synthesis of macrocycle **6.41** by RCM of diyne substrates

The stereochemical issue (*E/Z* isomerisation) in the RCM of the diene precursors for the synthesis of macrocyclic lactams, was solved by the advent of alkyne metathesis/Lindlar's reduction sequence.<sup>47</sup> This allowed the synthesis of a number of biologically active alkaloids, which were otherwise difficult to synthesize by RCM of dienes (as this will give a mixture of *E* and *Z* isomers). For example, diyne metathesis-Lindlar's reduction sequence was successfully used by Fürstner group in the synthesis of aza-macrolides (**6.44a-b**) (Scheme 6.15).<sup>47</sup> The diyne precursors to the aza-macrolides **6.42a-b** were treated with Schrock's precatalyst **6.40**<sup>45</sup> to give the alkyne macrocycles **6.43a-b** in good yields, which then underwent reduction in the presence of Lindlar's catalyst to give the desired **6.44a-b**.



Scheme 6.15: Synthesis of aza-macrolides **6.44a-b** by RCAM/Lindlar's reduction.

Fürstner *et al.* also used ring closing alkyne metathesis/Lindlar's protocol for the synthesis of biologically active marine alkaloid latrunculin B (**6.47**) (Scheme 6.16).<sup>48</sup> The Molybdenum catalyst **6.45** was used to affect the cyclization of the diyne precursor to give the alkyne macrocycle (**6.46**), which gave the desired alkaloid **6.47**.



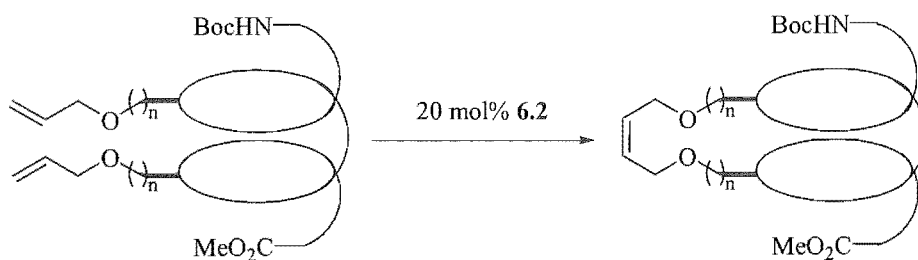
Reagents and conditions: i) **6.45** [ $\text{Mo}\{\text{N}(t\text{-Bu})(3,5\text{-Me}_2\text{C}_6\text{H}_3)\}_3$ ] (5 mol%), toluene, DCM,  $80^\circ\text{C}$ , 70% ii)  $\text{H}_2$ , Lindlar's catalyst, DCM, quant. iii) CAN, MeCN/ $\text{H}_2\text{O}$ , 78%.  
CAN=ceric ammonium nitrate.

Scheme 6.16: Synthesis of marine alkaloid **6.47** via diyne RCM, Lindler's reduction sequence.

## 6.4 Miscellaneous Applications of RCM

The scope of RCM metathesis has been extended to the synthesis of natural products, macrocyclic peptidomimetics and aminosugars in solution phase, as well as in solid phase and in nanotechnology. Here, a few recent examples in the development of RCM are described.

Blackwell and Grubbs<sup>49</sup> have used RCM in the synthesis of covalently cross-linked short peptide sequences **6.48a-b** to initiate helix formation (Scheme 6.17).

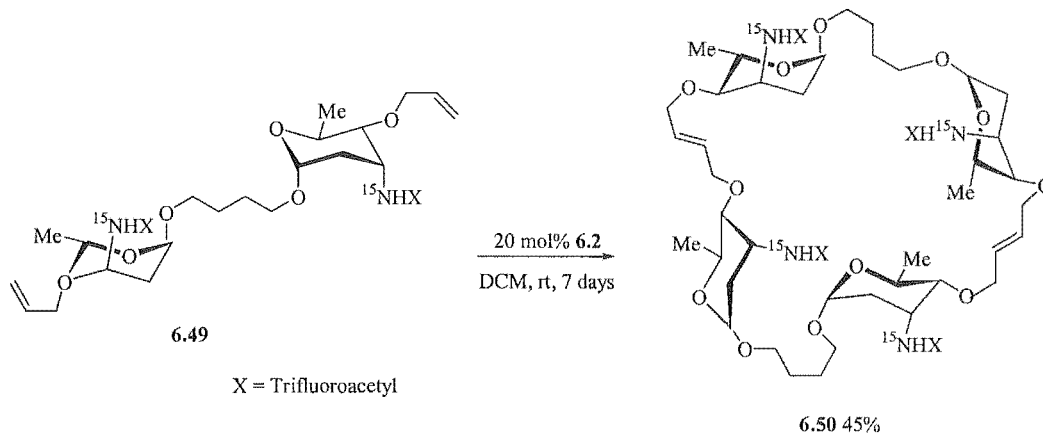


**6.48a** = Boc-Val-Ser-Leu-Aib-Val-Ser-Leu-OMe,  $n = 1$ , 85%

**6.48b** = Boc-Val-HSe-Leu-Aib-Val-HSer-Leu-OMe,  $n = 2$ , 90%

Scheme 6.17: Synthesis of helical peptide **6.48a-b** by RCM.

RCM has also been used in the synthesis of macrocyclic aminoglycosides, e.g. in the synthesis of 1,4-butanediol linked  $^{15}\text{N}$ -labelled aminoglycosides (**6.50**) from diene linker **6.49**, which can be used as probes for binding to RNA and other biomacromolecules (Scheme 6.18)<sup>50</sup>.



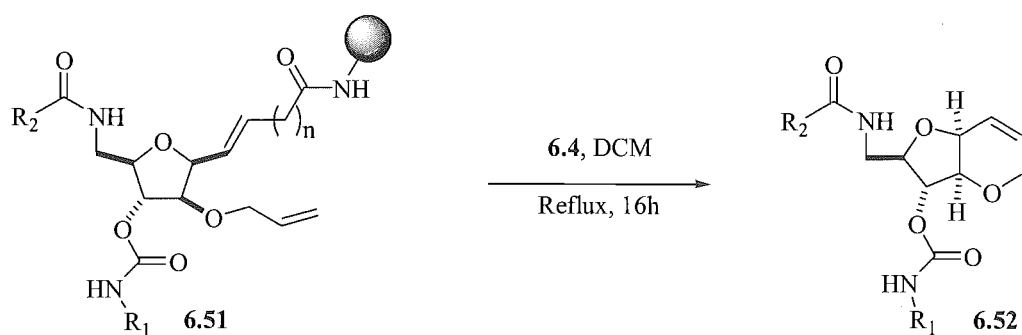
Scheme 6.18: Synthesis of aminoglycoside **6.50** by RCM.

The tetrasaccharide **6.50** is thought to have formed by the dimerization of the starting diene **6.49** to give an intermediate linear tetra-saccharide, which then cyclizes to the cyclo-aminoglycoside **6.50**; and that the axial amido substituent prevents the direct intramolecular olefin metathesis reaction. In addition to the cyclotetrasaccharide **6.50**, 5% of hexa-



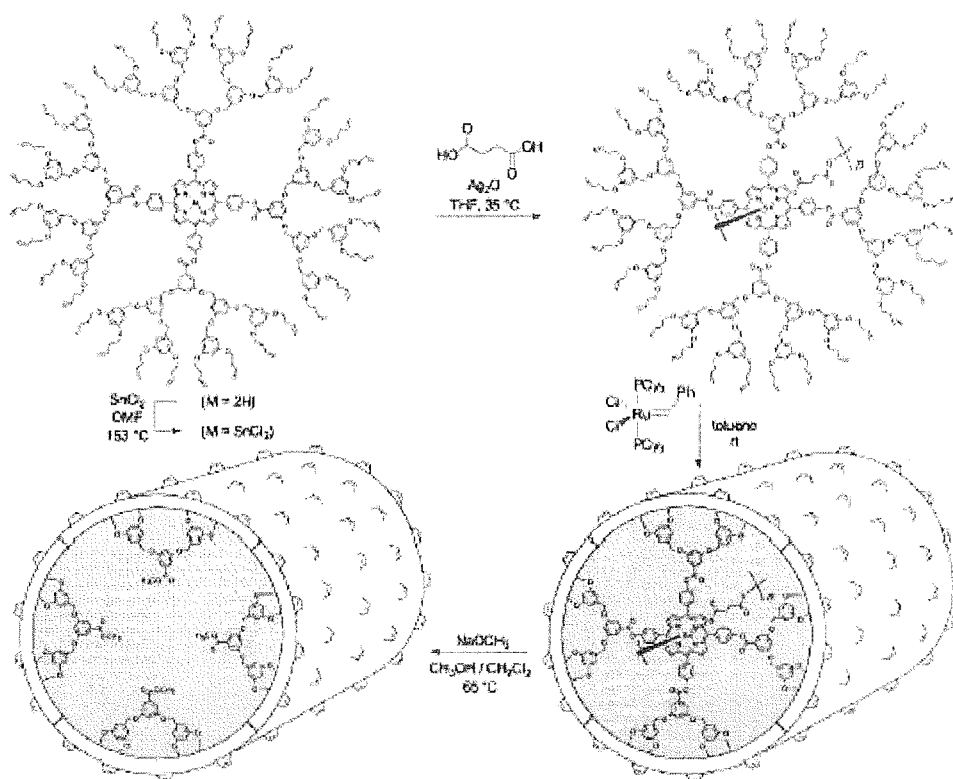
saccharide was also formed, which is thought to be formed by trimerization of the starting diene **6.49**.

Olefin metathesis has emerged as a versatile technology for combinatorial and parallel synthesis in solution as well as on solid-phase.<sup>51</sup> Recently, Timmer *et al.*<sup>52</sup> reported an interesting strategy for the construction and use of fused mannitol-derived oxacycles as combinatorial library scaffolds based on a RCM/resin cleavage approach (Scheme 6.19).



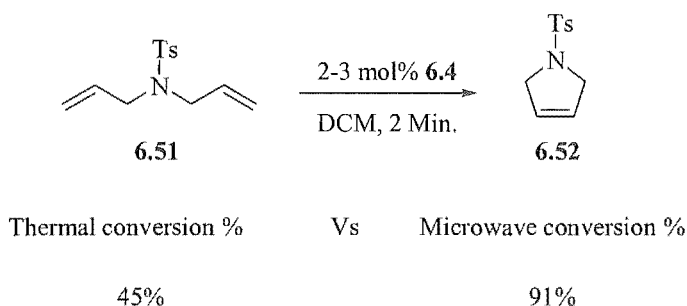
Scheme 6.19:

RCM has found interesting applications in the field of dendrimer chemistry. Zimmermann *et al.*<sup>53</sup> have used Grubbs' catalyst **6.2** in the controlled synthesis of nanotubes (Scheme 6.20)



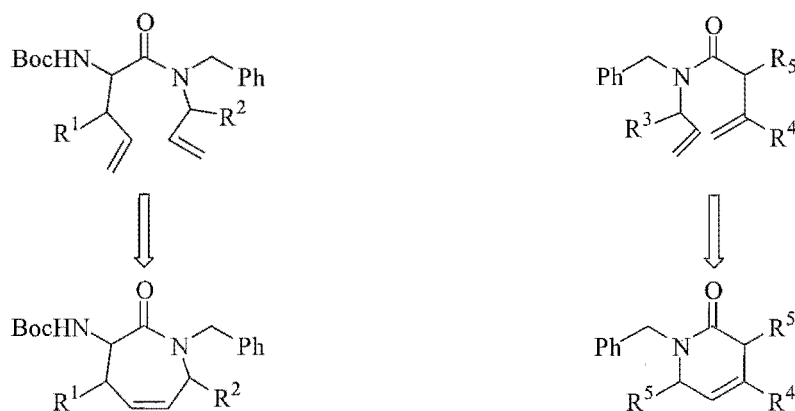
Scheme 6.20

More recently, RCM in the presence of microwave radiation has made progress, in accelerating the rate of RCM reactions.<sup>54</sup> For example the ring-closure of **6.51** to **6.52** in the absence of microwave radiation resulted in only 45% conversion of the starting diene to the cyclic product, whereas in the presence of microwave, 91% conversion of the substrate to the product occurred (Scheme 6.21).<sup>55</sup>



Scheme 6.21: Comparison of the % conversion of **6.51** to **6.52** in the presence/or absence of microwave radiation.

All these applications demonstrate that there is substantial potential for heterocyclic synthesis by RCM. Incremental improvements in catalyst effectiveness have rendered cyclic compounds that were once considered too complex for synthesis, readily accessible by RCM. Although alternate syntheses could be carried out, but the high versatility and functional group tolerance of the metathesis catalysts have made a concise and convenient route possible to the compounds accessible by other complex and multistep route. Due to this versatility and convenience of this method, we focused our research work on the synthesis of seven and six-membered amino acid derived lactams using RCM methodology (Scheme 6.22), which will be discussed in detail in chapter 7.



Scheme 6.22: Application of RCM to the synthesis of 7 & 6-membered  $\delta$ -lactams

## 6.5 References for Chapter Six

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## **CHAPTER SEVEN**

### **SYNTHESIS OF LACTAM ANALOGUES OF CYCLIC UREAS BY RING CLOSING METATHESIS AND THEIR DERIVATIZATION**



## 7.1 Introduction

There is significant interest in the synthesis of heterocyclic compounds for use as HIV protease inhibitors, for example cyclic ureas and analogues based on lactams. We present here a ring closing metathesis approach to the synthesis of such lactams and a subsequent Sharpless asymmetric dihydroxylation protocol for the synthesis of *cis*-diol analogues, which could prove potent HIV protease inhibitors.

The human immunodeficiency virus (HIV) has infected almost 38 million people worldwide,<sup>1</sup> and is the cause of the deadly disease AIDS.<sup>2</sup> It is classified as a retrovirus<sup>3</sup> and its pathogenicity is due to the virus attacking components of immune system such as T cells and macrophages.<sup>4</sup> This affects the immune system of those infected resulting in an increased susceptibility, to secondary infections such as *pneumocystis carinii* pneumonia and toxoplasmosis, which are often the cause of AIDS related deaths.

During replication, HIV encodes an essential aspartic protease,<sup>5</sup> that cleaves the *gag* and *gag-pol* viral polyproteins into four replicative enzymes and four structural proteins.<sup>2,3</sup> This protease is essential for the assembly and maturation of infectious virions. Inactivation of HIV protease by a single mutation of the Asp25 residue in the active site results in noninfectious virions,<sup>6</sup> and this led to targeting of HIV protease inhibition as an important strategy for the therapeutic treatment of AIDS.<sup>7a-b</sup> The HIV protease is a member of a class of aspartic proteases. Other aspartic proteases that catalyze the hydrolysis of amide bond via aspartate residues in the active site, include renin and pepsin. An enormous effort has gone into developing renin inhibitors as antihypertensive drugs, based on the mechanism of action of aspartyl proteases. Many of the principles established in these efforts were subsequently applied to the design of HIV protease inhibitors.

The rational design of the HIV protease inhibitors has been aided significantly by the availability of the three dimensional X-ray crystal structures of HIV protease in its native form,<sup>8</sup> and numerous inhibitor complexes.<sup>9</sup> The inhibitor-free structure of the HIV-1 protease (Figure 7.1) contains two identical amino acid chains, each with 99 residues. The two chains are interdigitated to form a  $\beta$ -sheet at the dimer interface. The molecule has an exact  $C_2$  symmetry and the catalytic site of the protease is located at the bottom of a large cavity in the middle of the protease as defined by both subunits. Two flexible flaps are formed by residues 45 to 56 in each monomer, and these open to allow the incoming polypeptide, over the top of the cavity.

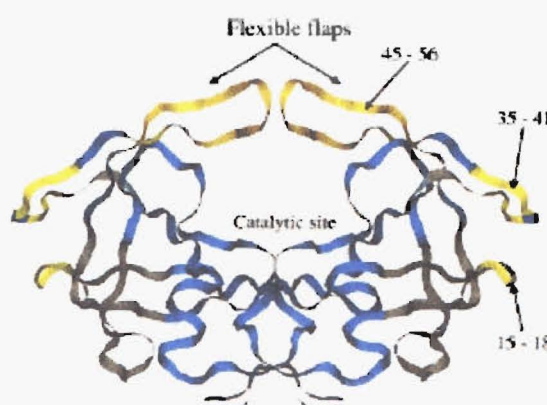
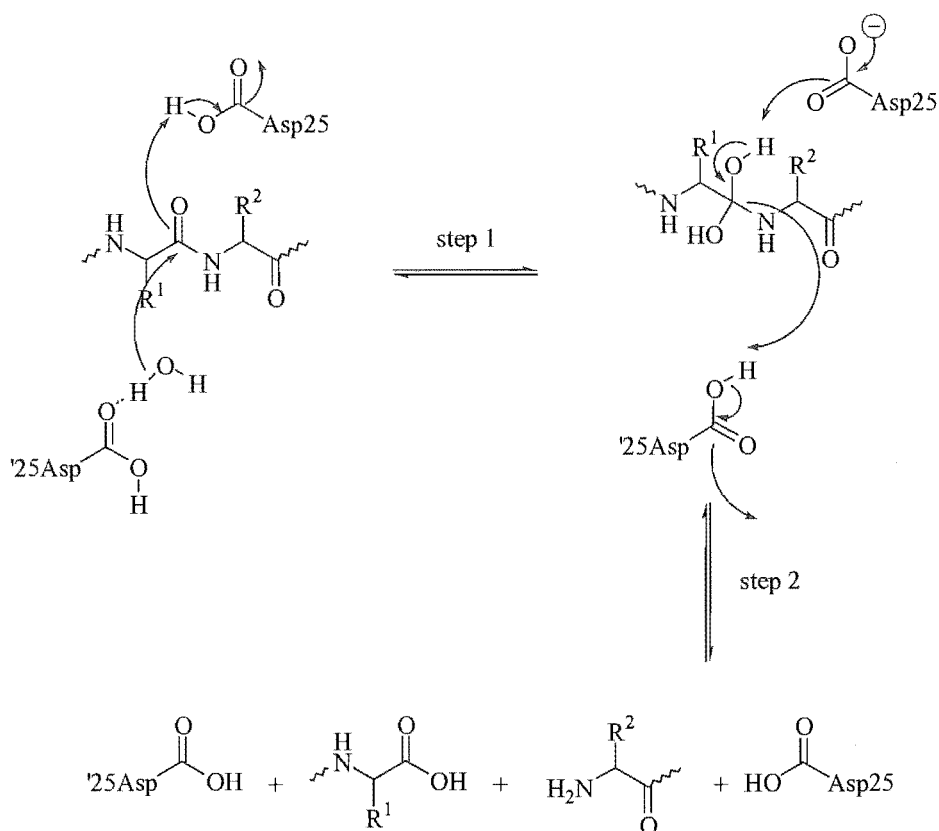


Figure 7.1: Structure of the HIV protease illustrating the two flexible flaps and the catalytic site of the enzyme

The enzyme's  $C_2$  axis lies between, and perpendicular to, the catalytic aspartyl residues Asp25 and Asp25'. One aspartyl residue acts as a base initiating nucleophilic attack on the scissile amide bond of the substrate using an active site water molecule. The other aspartate is thought to act as an acid stabilizing the carbonyl oxygen in tetrahedral intermediate (Scheme 7.1). HIV protease cleaves its substrate at specific sites, of which at least eight have been identified in the polyproteins, with a variety of amino acids adjacent to the scissile bond.<sup>7a,10</sup>



Scheme 7.1: Aspartic protease hydrolysis of an amide bond.

Studies<sup>11</sup> have shown that a potent HIV protease inhibitor requires a hydrophobic P1/P1' substituent (such as benzyl) to occupy the complementary HIV protease specificity pockets (S1/S1'),<sup>†</sup> and a lipophilic heterocycle at P2/P2' position to occupy the secondary specificity pocket (S2/S2'), as well as groups capable of forming hydrogen bonds in the active site of the HIV protease. The resistance profile against mutant HIV strains is also improved by increasing the number of hydrogen bonds to Asp29, Asp30 and Gly48 in the HIV active site.<sup>11</sup>

<sup>†</sup> Using Schechter-Berger nomenclature<sup>12</sup> (see Figure 7.2 on the next page), where the residues on the amino-terminal side of the cleaved bond are denoted as P1-Pn, and those on the carboxy-terminus are denoted P1'-Pn' (with the corresponding sub sites on the enzyme denoted as Sn-Sn').

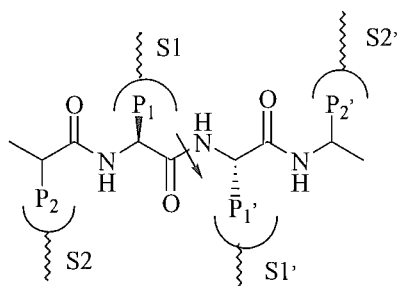


Figure 7.2: Schechter-Berger nomenclature for labelling positions around the substrate cleavage site and specificity pockets of the enzyme.

Based on the  $C_2$  symmetry, a number of HIV protease inhibitors have been designed and synthesized. The most successful and impressive example<sup>13</sup> uses a diol to act as a transition state mimic. The initial key linear inhibitors synthesized were **7.1**-**7.3**.<sup>13</sup> **7.1** and **7.2** were found to be active against HIV with  $IC_{50} = 500$  nM and  $IC_{50} = 220$  nM respectively. Thus, numerous analogues of **7.2** with different substituent patterns were synthesized and screened, to identify **7.3** as a particularly potent compound with an  $IC_{50} = 0.24$  nM (Figure 7.3). Unfortunately, these types of inhibitors are not particularly soluble in aqueous media, and thus have poor bioavailability.

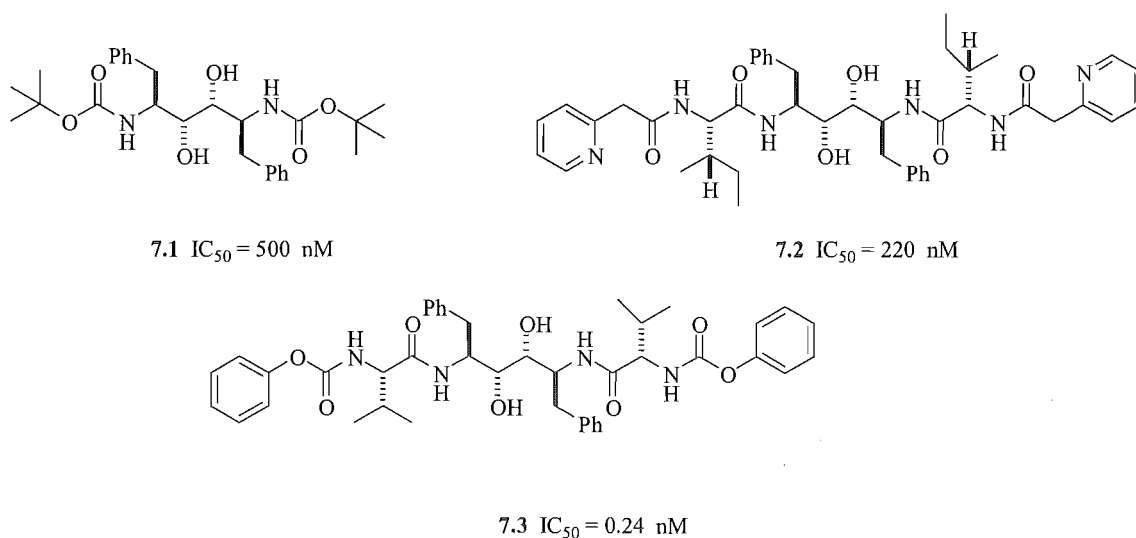


Figure 7.3: Dihydroxyethylene based transition state mimetics as HIV protease inhibitors

Subsequent work revealed another linear potent HIV protease inhibitor **7.4**<sup>14,15</sup> and its X-ray crystal structure bound to HIV protease was investigated by Wlodawer<sup>8</sup> to reveal that the hydrophobic side chains bind to the C<sub>2</sub> symmetric HIV protease in extended conformation with extensive hydrogen bonding interactions with the enzyme backbone amides (Figure 7.4). A key feature of all these potent HIV protease inhibitors is the hydrogen bonding from two central carbonyls to a water molecule which bridges the Ile50 and Ile150 residues in the flaps of the enzyme.

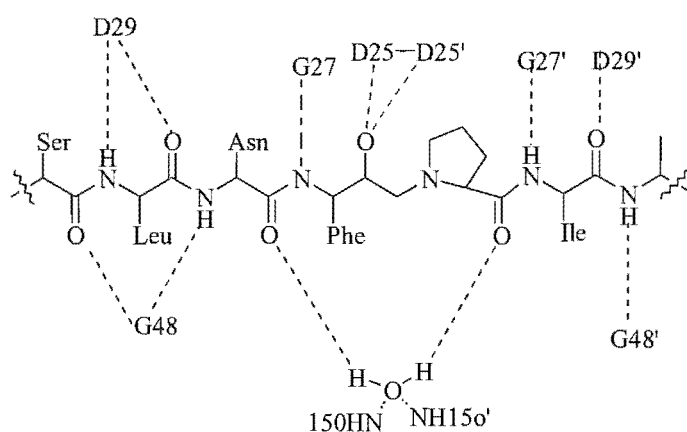


Figure 7.4: Observed hydrogen bonding in crystal structure of **7.4**.

The main problem with the aforementioned inhibitors is their high molecular weight, lack of selectivity, poor antiviral activity and poor oral availability. Consequently, a new search for low molecular weight, conformationally constrained inhibitors was initiated.

The search for inhibitors with greater potency *in vivo*, and improved resistance profiles, led to the rational design of cyclic urea HIV protease inhibitors.<sup>16</sup> Cyclic urea inhibitors were designed to mimic the hydrogen bonding in the X-ray crystal structure of HIV protease inhibitors. The binding mode of the cyclic ureas to the HIV protease inhibitors involves the replacement of the active site water molecule with the urea oxygen, as well as interaction of the diol oxygens with the aspartyl residues.<sup>17</sup> Schechter-Berger<sup>12</sup> nomenclature (see Figure

7.2 earlier) describes the interactions of HIV-protease with its cyclic urea inhibitors (Figure 7.5).

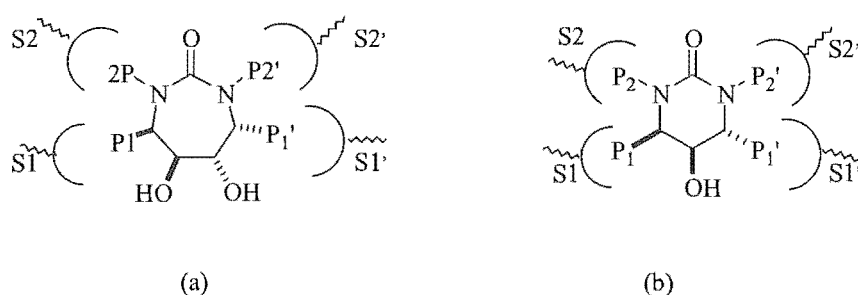
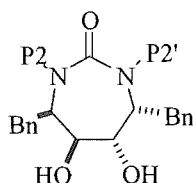


Figure 7.5: Schester-Berger nomenclature used to describe the interactions of HIV protease and its cyclic ureas inhibitors.

The rigid cyclic scaffold of urea based inhibitor allows optimal binding interactions of the P1/P1' and P2/P2' residues with their corresponding S1/S1', S2/S2' pockets in the active sites (Figure 7.5). Table 7.1 summarizes structure-activity relationship studies of some of the lead symmetric cyclic ureas developed by Lam *et al.*<sup>17</sup>

Table 7.1: P2/P2' SARs of symmetric cyclic ureas 7.4.



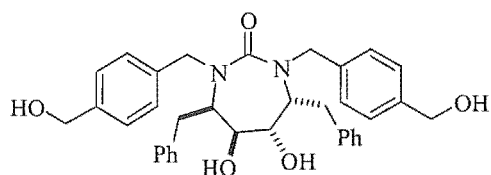
Cyclic Ureas 7.4

P2/P2'	K <sub>i</sub>	IC <sub>90</sub>
Allyl	5.2	4.7
Cyclopropylmethyl	2.1	1.8
<i>p</i> -hydroxymethylbenzyl (DMP323)	0.34	0.057
<i>m</i> -aminobenzyl.2CH <sub>3</sub> SO <sub>3</sub> H (DMP450)	0.28	0.13
<i>m</i> -aldoximebenzyl	0.01	0.005
<i>m</i> -acetoximebenzyl	0.01	0.002

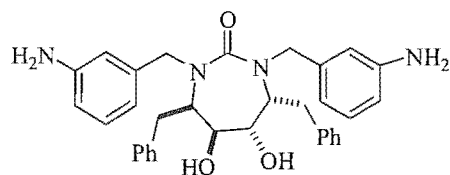
A number of HIV protease inhibitors have been approved by FDA for use in AIDS therapy, including cyclic urea based inhibitors, **7.5** (DMP 323) and **7.6** (mozanavir, DMP 450) as well as linear inhibitors like **7.7** (Saquinavir)<sup>18</sup> and **7.8** (Amprenavir)<sup>19</sup> (Figure 7.6).

A major problem with these inhibitors is the resistance by different variants of the HIV to these inhibitors.<sup>4,20,21</sup> One possible way of overcoming this problem is to use combination therapy, in which a number of drugs are used concurrently to treat a patient. Unfortunately, mutant strains resistant to **7.7** (Saquinavir) and **7.8** (Amprenavir) have appeared, whereas **7.5** (DMP 323) was rejected for further clinical trials based on poor solubility, and highly variable oral availability. Fortunately, mozanavir **7.6** (DMP 450) shows substantial oral bioavailability observed in all species examined, including man.<sup>22</sup> Compound **7.6** has been

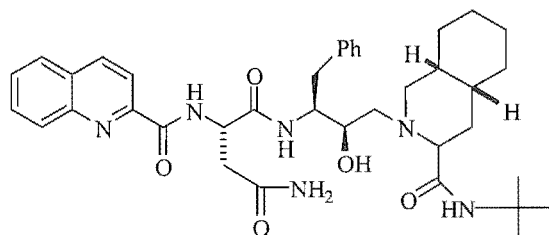
the subject of phase I/II dose escalating clinical studies and appears to have good antiviral activity and tolerability at all doses tested. However, the plasma level at trough with multiple dosing procedure fall short of the concentration required for all HIV mutants.



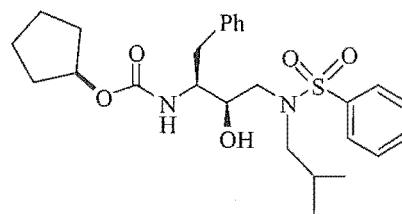
7.5 DMP 323  $K_i = 0.34$  nM



7.6 DMP 450  $K_i = 0.28$  nM



7.7 Saquinavir  $K_i = 0.12$  nM



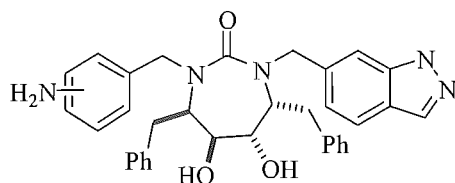
7.8 Amprenavir  $K_i = 0.60$  nM

Figure 7.6: FDA approved HIV protease drugs.

Further cyclic ureas analogues have been developed by modification of functional groups at the P1/P1' and P2/P2' positions. However, due to the low solubility of the symmetric cyclic ureas, and consequently the low oral bioavailability, research has recently been diverted to the synthesis of non-symmetrical cyclic urea analogues with better bioavailability.<sup>23</sup>

De Lucca *et al.*<sup>23</sup> synthesized the first non-symmetric cyclic urea protease inhibitors analogues (Figure 7.7), e.g. 7.9-10. However, the resistance profile of these inhibitors against different HIV mutants was again not sufficient for a sustained antiviral effect in man.



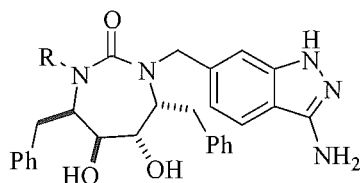


3-NH<sub>2</sub> = **7.9** K<sub>i</sub> = 0.03 IC<sub>50</sub> = 11 bioavailability = 93% (F)

4-NH<sub>2</sub> = **7.10** K<sub>i</sub> = 0.03 IC<sub>50</sub> = 11 bioavailability = 100% (F)

Figure 7.7: Non-symmetric cyclic ureas

Subsequently, Rodgers *et al.*<sup>24</sup> reported the synthesis of DMP analogues DMP 850 (**7.11**) exhibiting K<sub>i</sub> of 0.031 and DMP 851 (**7.12**) exhibiting K<sub>i</sub> of 0.021 nM respectively, and these show modest potency in a whole cell antiviral assay with an IC<sub>90</sub> of 62 and 56 nM, respectively (Figure 7.8).



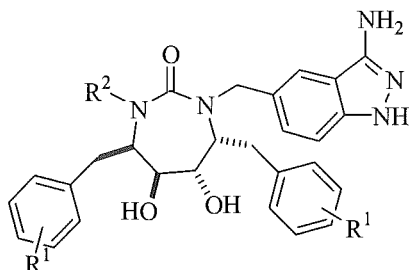
R = Benzyl DMP 850 **7.11** K<sub>i</sub> = 0.03 nM IC<sub>90</sub> = 62 nM

R = n-Butyl DMP 851 **7.12** K<sub>i</sub> = 0.02 nM IC<sub>90</sub> = 51 nM

Figure 7.8: Non-symmetric cyclic ureas DMP 850 and DMP 851

Kaltenback *et al.* further modified the P1/P1' groups<sup>25</sup> of the nonsymmetrical 3-aminoidazoles DMP 850 and DMP 851, to increase their lipophilicity, thus improving their antiviral potency against wild type HIV (see Table 7.2). Based on the resistance profile against HIV mutants, the P1/P1' substituted 3-methyl or 4-methyl analogues of DMP 850 and DMP 851 are approximately equipotent. However, their poor oral bioavailability outweighed the improvements in the antiviral potency, eliminating these substituted analogues as potential development candidates.

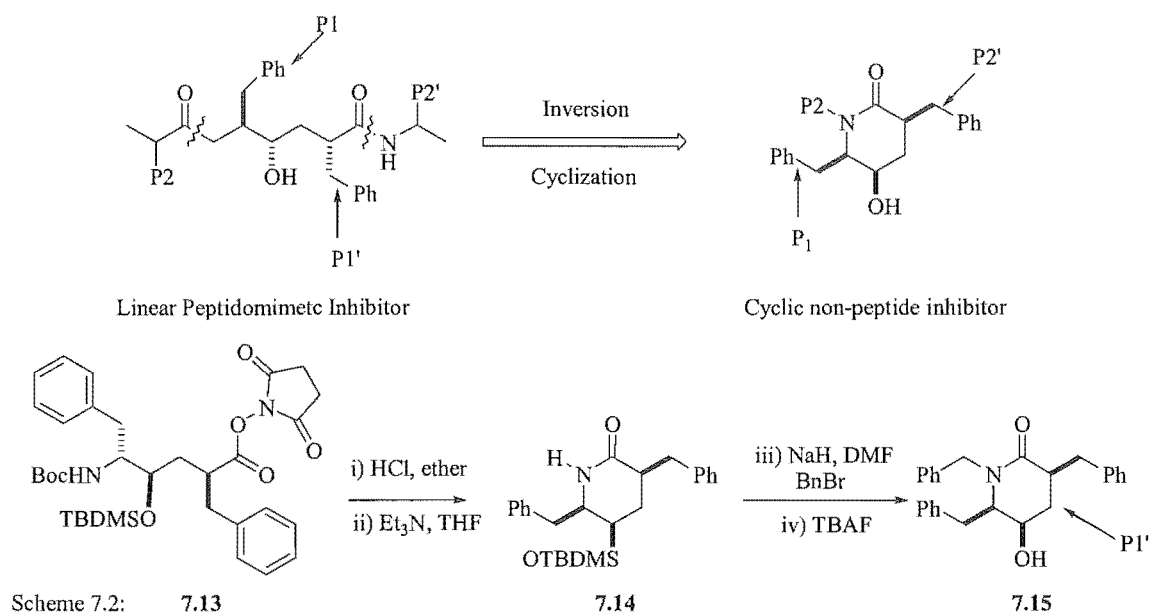
Table 7.2: Structure activity relationship studies of P1/P1' substituted cyclic ureas



Compound	R <sup>1</sup>	R <sup>2</sup>	K <sub>i</sub> (nM) <sup>a</sup>	RF IC <sub>90</sub> (nM)	HXB2 IC <sub>90</sub> (nM)
DMP 850	H	Bn	0.031	62	92
	3-CH <sub>3</sub>	Bn	0.062	25	26
	4-CH <sub>3</sub>	Bn	0.047	12	17
DMP 851	H	<i>n</i> -Bu	0.021	56	69
	4-CH <sub>3</sub>	<i>n</i> -Bu	0.045	31	54
	3-CH <sub>3</sub>	<i>n</i> -Bu	0.037	12	16

a: Determined by measuring the accumulation of RF-wild type viral RNA transcript after infection of cells with HIV-1

Subsequent research in this area has been focused on the synthesis of non-symmetric cyclic urea analogues and related N-heterocyclic analogues. For example, De Lucca reported the synthesis of a  $\delta$ -lactam<sup>26</sup> **7.15** as heterocyclic analogues of the urea-based HIV protease inhibitors. Synthesis of **7.15** utilized the hydroxyl ethylene isostere based linear inhibitor **7.13**, by first inverting the stereocentres and subsequent cyclization of the carboxyl terminus into the amino terminus to give the corresponding **7.14**, which is finally benzylated and desilylated to give **7.15** (Scheme 7.2). However, this synthetic methodology does not permit the convenient introduction of a P1' substituent into the cyclic inhibitor.



The lactam **7.15** generated in this way has only modest potency, which has been linked to the lack of the P1' group (Figure 7.9a). The importance of a P1' substituent for optimum potency is evident by a comparison of the corresponding six-membered cyclic urea analogues that possess (for example, Figure 7.9b) or lack (for example, Figure 7.9c) the P1' substituent. The absence of a P2' substituent in the six-membered cyclic urea analogue, however, shows only a moderate loss of potency (Figure 7.9d) compared to one caused by the absence of a P1' substituent (Figure 7.9c). Consequently, this synthetic methodology limits the investigation of potential  $\delta$ -lactams inhibitors.

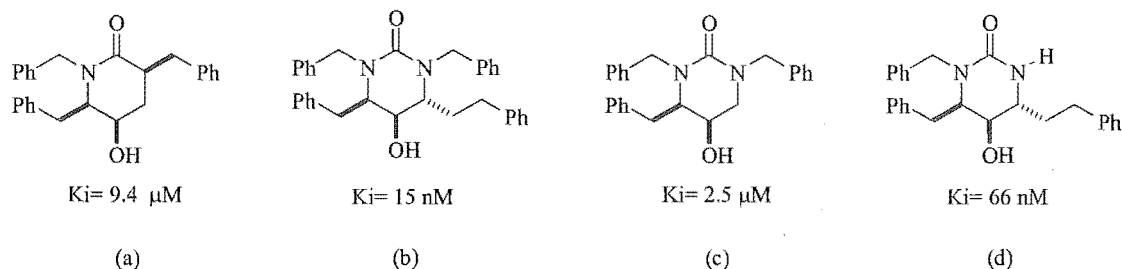
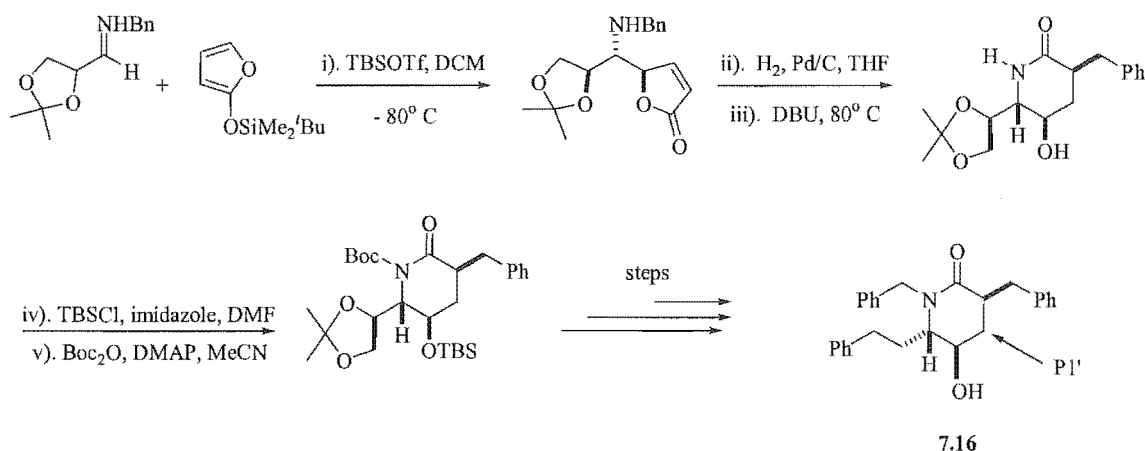


Figure 7.9: Comparison of  $K_i$ s for lactam and pyrimidinones

Battistini *et al.*<sup>27</sup> have reported the synthesis of the six membered lactam **7.16** using a vinylogous version of Mannich type addition as the key reaction in their synthesis (Scheme 7.3). This synthetic target **7.16**, again lacks the P1' substituent and is formed after a tedious multistep synthesis.



Scheme 7.3: Synthesis of lactam **7.16** via vinylogous Mannich reaction

Research in our laboratories has focused on the synthesis of six-membered piperidinones using ring closing metathesis methodology as the key step (Scheme 1.6, chapter 1)<sup>28</sup> leading to the formation of lactam **7.15** that also lacks a P1' substituent required for optimum potency.

It is clear from the above discussion that there is still a need for convenient and general method of the synthesis of appropriately substituted, potent and selective protease inhibitors. The corresponding seven-membered lactams proposed in Figure 7.10 are less symmetrical, and may improve the unfavourable solubility and the resistance profile that is the general characteristic of many protease inhibitors.

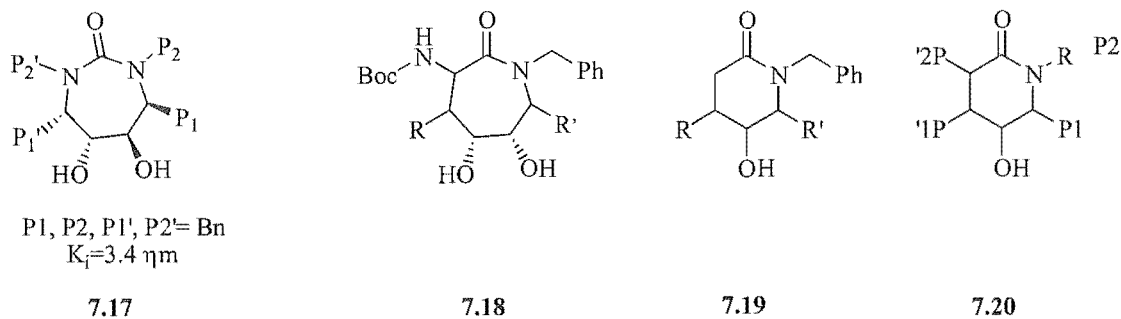


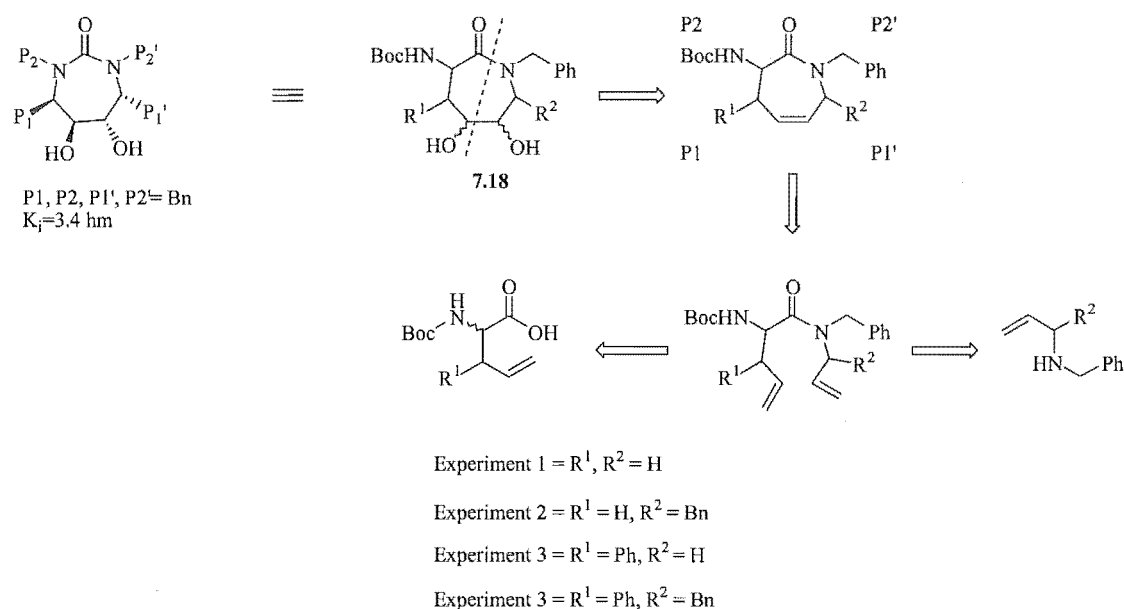
Figure 7.10: Seven and six-membered lactam analogue 7.18, 7.19, and 7.20 of cyclic urea 7.17

The target seven-membered lactam inhibitors can be synthesized with a variety of substituents at R and R' positions (discussed in detail in sections 7.4 & 7.5). The N-*t*-butyloxycarbonyl group in analogues of 7.18 can be easily deprotected and the resulting free amine could be coupled to other amino acids to give potent HIV protease inhibitors. The six-membered  $\delta$ -lactams prepared previously in this laboratory do not contain P<sub>1</sub>' substituent.<sup>28</sup> Research has therefore been focused on the synthesis of  $\delta$ -, and  $\epsilon$ -lactams analogues 7.19 containing the P<sub>1</sub>' substituents.

The remainder of this chapter describes the research on the design and synthesis of seven-membered peptidomimetics-derived lactams (Figure 7.10), as well as the attempted synthesis of six membered lactam analogues of cyclic urea HIV protease inhibitors. The main aim of the research work described here is to develop a general methodology for the synthesis of substituted lactam HIV protease inhibitors. The key feature of this synthetic approach is the ring-closing metathesis reaction, that is used to generate an olefinic lactam from a diene. The derivatization of the resulting lactam is investigated to assess the feasibility of using this method to synthesize specific lactam HIV protease inhibitors.

## 7.2 Synthetic Plan for the Synthesis of Seven-Membered Lactam Rings and their Derivatization

Four experiments were designed to synthesize seven-membered lactam analogues of cyclic urea protease inhibitors with varying P1, P2, P1' and P2' substituents. Retrosynthetic analysis of the target molecule **7.18** (Scheme 7.4) suggests that the appropriately substituted acid and amine (corresponding to P1 and P1' positions of the respective urea analogues), could be used as starting molecules for the preparation of the key diene, the substrate for ring closing metathesis.



Scheme 7.4: Retrosynthetic Analysis for the synthesis of target molecules

The olefinic lactam could be synthesized from the respective diene using ring closing metathesis (Scheme 7.4). The olefinic lactam can then be functionalized to the *cis*-diol **7.18**, using Sharpless dihydroxylation procedure. This sequence provides a convenient and general protocol for the synthesis of the target lactam-based HIV protease inhibitors. What follows is a brief introduction of the Sharpless asymmetric dihydroxylation.

### 7.3 Sharpless Asymmetric dihydroxylation reaction

The diastereospecific *cis*-dihydroxylation of alkenes using osmium tetroxide as developed by Sharpless and co-workers<sup>29</sup> is a valuable synthetic procedure for the introduction of a vicinal diol moiety into a molecule. The reaction utilizes catalytic quantities of osmium tetroxide [(or  $\text{K}_2\text{OsO}_2(\text{OH})_2$  as a non-volatile source of osmium that generates  $\text{OsO}_4$  *in situ*)] and a chiral amine ligand in conjunction with potassium ferricyanide and potassium carbonate [ $\text{K}_3\text{Fe}(\text{CN})_6\text{-K}_2\text{CO}_3$ ] as stoichiometric reoxidants in a biphasic solvent medium (*t*-BuOH/ $\text{H}_2\text{O}$ ). The most commonly used ligands in this regard are cinchona alkaloid based ligands **7.21** and **7.22**,<sup>30</sup> DABCO based ligand **7.23**,<sup>31</sup> chiral diamine ligands **7.24**,<sup>32</sup> **7.25**,<sup>33</sup> **7.26**<sup>34</sup> and **7.27**<sup>35</sup> as depicted in Figure 7.11.

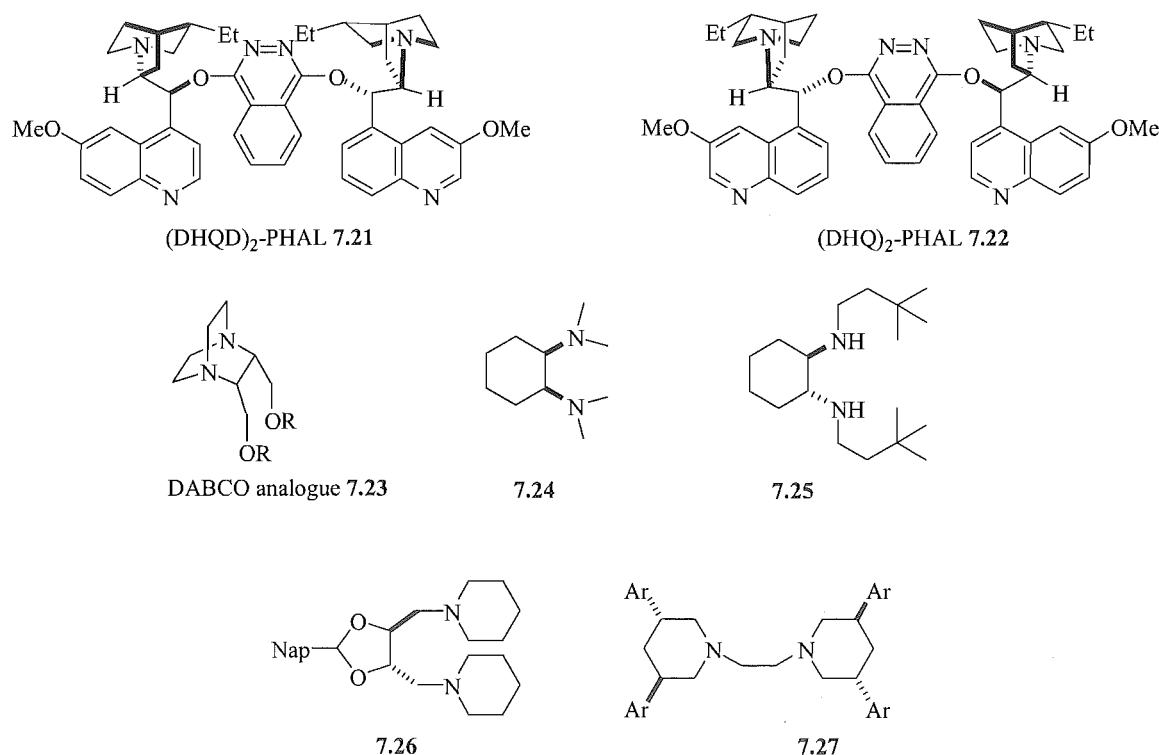


Figure 7.11: Ligands used in the asymmetric dihydroxylation reaction.

The catalytic cycle for this reaction is illustrated in Figure 7.12. Coordination of the chiral amine ligand to the osmium results in the formation of a chiral monoglycolate osmate complex. This complex can distinguish between the prochiral faces of a substrate alkene, resulting in *cis*-diol formation on one face in preference to the other. This selectivity is controlled by a few factors including the structure of chiral amine ligand and the structure of the alkene substrate. Opposite enantiomers of the chiral tertiary amine afford opposite enantiomers of a *cis*-diol. The complex then hydrolyzes releasing the diol and the ligand into the organic phase while the resulting Os(IV) species finds its way in to the aqueous phase.<sup>36</sup>

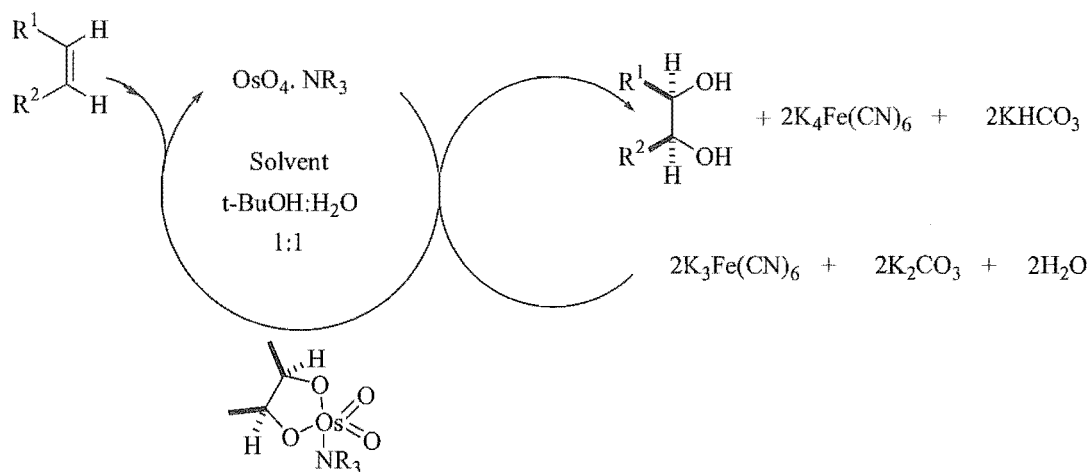




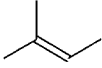
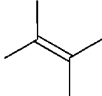


Figure 7.12: Catalytic cycle for Sharpless asymmetric dihydroxylation.

Sharpless has categorized the alkene substrates in this reaction into six general types varying in the degree and position of substituents (Table 7.3). Moderate to good levels of enantioselectivity can be achieved for most of these types of alkenes using the above mentioned phthalazine based ligand systems.



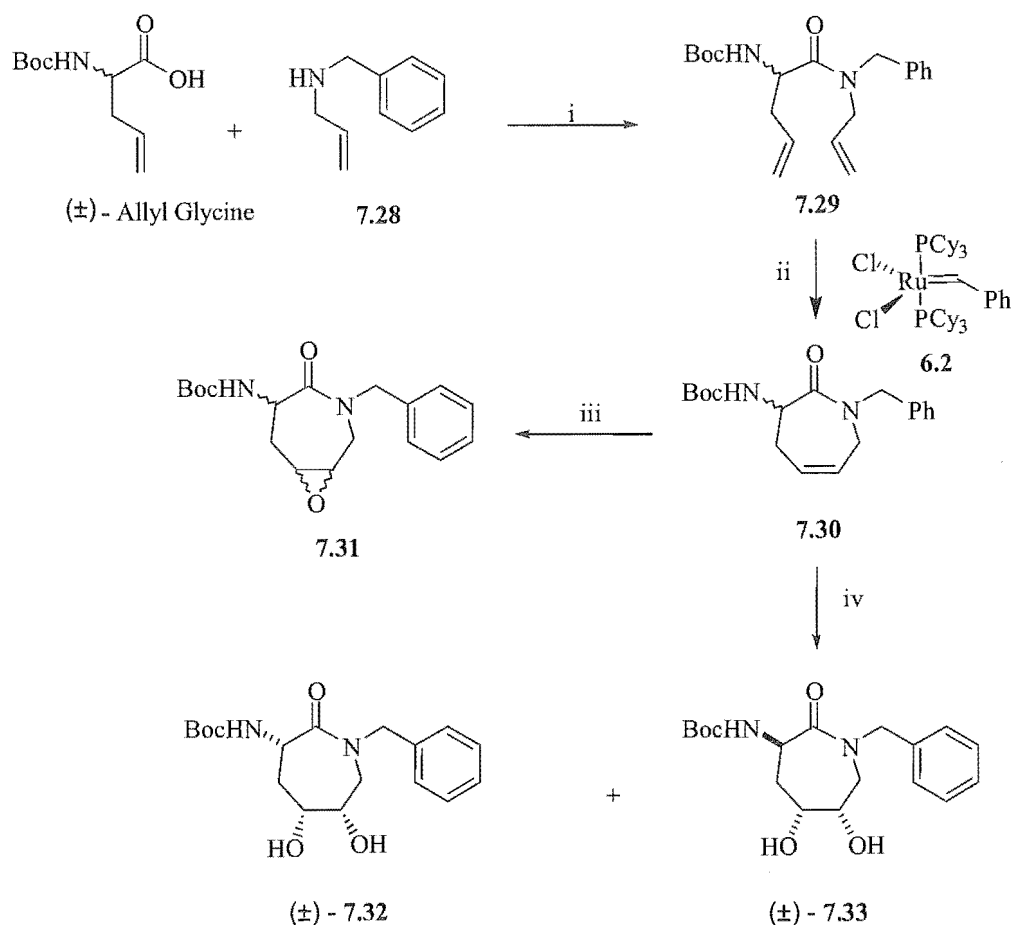
Table 7.3: Sharpless structure classification of alkenes

Class	I	II	III	IV	V	VI
Structure						

The alkene precursors to the diols (see Scheme 7.4) fall into class III, i.e. *cis*-disubstituted olefins, in this classification. What follows is a discussion about the synthesis of seven membered ring lactams and their derivatization.

#### 7.4 Experiment 1: Synthesis of Seven-membered Lactam mimetic from racemic Allyl Glycine having $P1/P1' = H$ , $P2 = NHBoc$ , $P2' = Bn$ :

The introduction of  $P2$ ,  $P2'$  substituents into the target seven-membered lactam (see 7.18 in scheme 7.4) was achieved by coupling of ( $\pm$ ) allylglycine with *N*-allyl benzyl amine 7.28 under standard peptide coupling conditions to give a rotameric mixture (5:2, determined by analysis of  $^1H$  NMR spectrum) of the diene 7.29 in 88% yield (Scheme 7.5).



Reagents and conditions: i) EDCI, HOBT, DIPEA, DCM, rt, 16h, 88%. ii) Grubb's catalyst **6.2**, DCM, reflux, 24h. 67-76% iii) Oxone, acetone, water, rt, 62%. iv) (DHQD)<sub>2</sub>PHAL or (DHQ)<sub>2</sub>PHAL, K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>Fe(CN)<sub>6</sub>, MeSO<sub>2</sub>NH<sub>2</sub>, 0°C-rt, 48h, 71-75%.

Scheme 7.5: Synthesis of Lactam **7.30** and its derivatives **7.31**, **7.32** and **7.33**.

The structure of the diene **7.29** was confirmed by <sup>1</sup>H, <sup>13</sup>C NMR and mass spectrometry. The <sup>1</sup>H NMR spectrum of the diene revealed the presence of two rotamers at rt (see Figure 7.13). The allylic protons attached to N are observed as multiplets at δ 2.31-2.54 ppm. The allylic protons attached to C<sub>α</sub> also show two multiplets in the range 3.89-4.08 ppm confirming the presence of two isomers. The benzylic protons for the major isomer appear as doublets at δ 4.48 and 4.71 ppm with a large coupling constant 14.5 Hz, whereas the

same protons for minor isomer resonated as a singlet at  $\delta$  4.61 ppm. The  $H_{\alpha}$  for the major isomer gave a multiplet at  $\delta$  4.64–4.68 ppm; and for minor isomer  $H_{\alpha}$  appear as a multiplet at  $\delta$  4.72–4.75. In addition, the olefinic protons gave multiplets at  $\delta$  5–6 ppm.

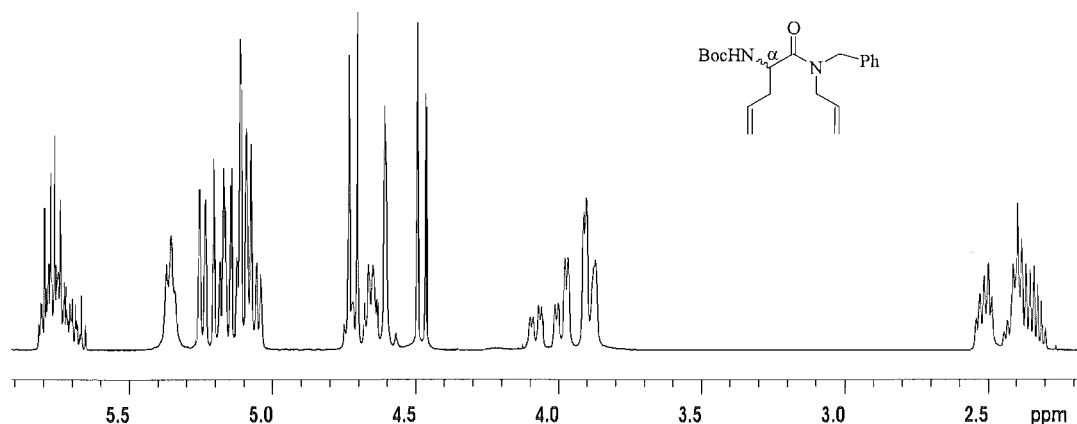


Figure 7.13: Portion of the  $^1\text{H}$  NMR spectrum (500 MHz) of **7.29**.

Further confirmation of **7.29** was made through high resolution mass spectrometry which revealed the observed  $[\text{MH}]^+$  of  $\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}_3$  was in agreement with the calculated one which is equal to 345.2178.

Ring closing metathesis of the diene **7.29** with Grubb's catalyst (**6.2**) in dry degassed DCM, then resulted in the formation of the desired seven-membered cyclic mimetic **7.30** in 67–76% yield (Scheme 7.5). The key  $^1\text{H}$ ,  $^{13}\text{C}$  NMR chemical shifts and the 2D COSY correlations, confirming the structural assignment of **7.30** are shown in Figure 7.14. Correlations observed between the NH and H-3 protons established the assignment of the exocyclic resonances. 2D correlations among H-3, H-4 methylene protons and H-5 olefinic protons confirmed connectivity of C-3, C-4 and C-5, while correlations between H-5 and H-6 olefinic protons assigned connection of C5 to C6. Similarly, 2D correlations between H-6 olefinic proton and H-7 methylene protons show the connection of C-6 and C-7. In addition, the 2DHSQC/DEPT experiment allowed the assignment of protonated carbons,

thus showing a prominent peak for *t*-Bu protons at 28.3 ppm, with C-4 at 33.3 ppm and C-7 resonating lower field at 45.1 ppm due to the proximity of N atom. Similarly, the olefinic carbons resonated at 124 ppm and 130 ppm as assigned by 2D HSQC/DEPT experiment, thus assigning the lactam as compound **7.30**.

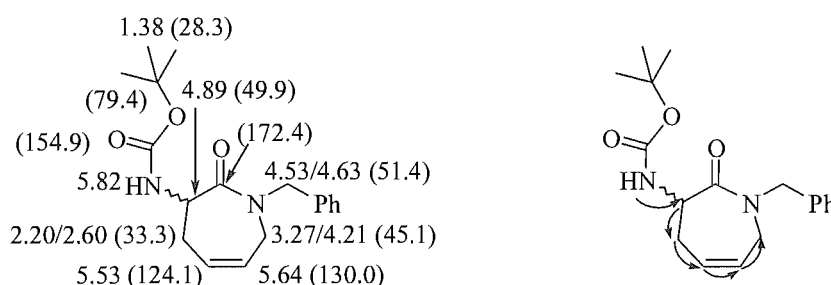


Figure 7.14: a) Key  $^1\text{H}$  and  $^{13}\text{C}$  NMR (in brackets) chemical shifts and b) connectivity data obtained from 2D COSY experiment for **7.30**

After the synthesis and characterization of the olefinic lactam **7.30**, the next step was functionalization of the ring bound olefin via epoxidation and *cis*-dihydroxylation. So, the olefinic lactam **7.30** was first subjected to epoxidation (as depicted in Scheme 7.5, step iii) using Oxone® and acetone/water mixture<sup>37</sup> to generate the dimethyldioxirane *in situ*, to give a diastereoisomeric mixture [(~1:1), determined from  $^1\text{H}$  NMR spectrum by the integration of *t*-Bu protons] of epoxides **7.31a** and **7.31b** (stereochemistry not assigned) in 63% yield (Figure 7.15). Further separation of the epoxides could not be achieved.

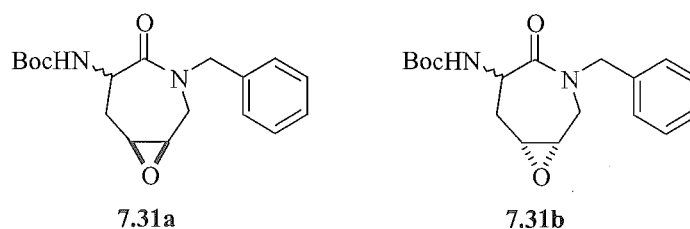
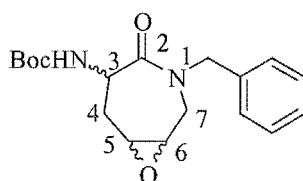


Figure 7.15: Two possible epoxides **7.31a** and **7.31b** from epoxidation of lactam **7.30**.

The key  $^1\text{H}$  NMR chemical shifts for the mixture of epoxides (**7.31a** and **7.31b**) are listed in Table 7.4. Analysis of the  $^1\text{H}$  NMR resonances showed that **H-3**, **H-5**, **H-6** and **H-7** resonated at higher field  $\sim 0.12$ - $0.17$  ppm for the one of the isomer as compared to the second isomer. The **NH** protons also show the same trend resonating  $\sim 0.13$  ppm higher field for one isomer compared the other one (see Table 7.4).

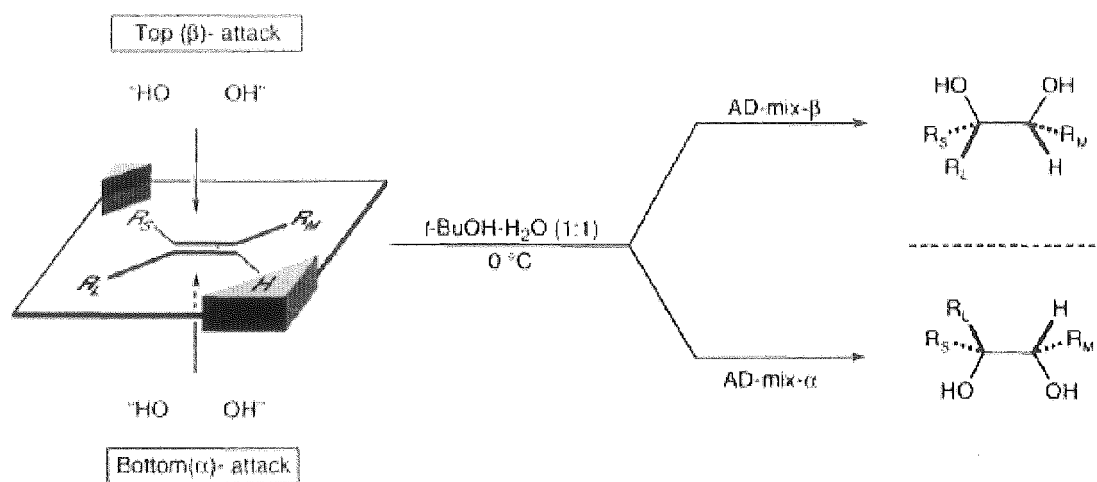
Table 7.4: Characteristic  $^1\text{H}$  NMR Chemical shifts of a mixture of epoxides **7.31a** and **7.31b**.



isomer	<b>H-4</b>	<b>H-7</b>	<b>CH<sub>α</sub></b>	<b>H-5</b>	<b>H-6</b>	<b>NH</b>
<b>7.31a/or b</b>	1.91/2.03	3.65/3.92	4.57	3.18	3.04	5.86
<b>7.31a/or b</b>	2.52/2.65	3.62	4.42	3.01	2.90	5.73

Efforts were then directed towards the derivatization of the double bond of the lactam **7.30** via catalytic Sharpless *cis*-asymmetric dihydroxylation using the known methodology for the AD of a *cis* double bond<sup>30</sup> (see Scheme 7.5, step d). The reaction was carried out using both bis cinchona alkaloid based ligands dihydroquinidine phthalazine [(DHQD)<sub>2</sub>-PHAL] **7.21** or dihydroquinine phthalazine [(DHQ)<sub>2</sub>-PHAL] **7.22**. In principle, the reaction with ligand **7.21** (AD-mix-β) should produce a diol obtained from top (β)-attack whereas with **7.22** (AD-mix-α)<sup>†</sup> should result in the formation of the diol from the opposite face<sup>30</sup> (Scheme 7.6).

†. The commercial names for the AD reagent containing ligand **7.21** with  $\text{K}_3\text{Fe}(\text{CN})_6$ ,  $\text{K}_2\text{CO}_3$ , and  $\text{K}_2\text{OsO}_2(\text{OH})_4$  are AD-mix-β and AD-mix-α containing ligand **7.22**.



Scheme 7.6: Predicted dihydroxylation in the presence of AD-mix- $\alpha$  and AD-mix- $\beta$ <sup>30</sup>

However, the reaction with either ligand (**7.21** or **7.22**) gave a diastereomeric mixture [(9:1), determined by analysis of  $^1\text{H}$  NMR spectrum by the integration of *t*-Bu protons] of *cis* diols **7.32** and **7.33**. The major isomer was separated as a white solid by fractional crystallization using PE/ $\text{CHCl}_3$ . The remaining filtrate contained a mixture of both isomers which could not be separated by column chromatography or further crystallization.

The configuration of the major diol ( $\pm$ )-**7.32** was assigned on the basis of a 2D NOE experiment as depicted in Figure 7.16, showing a *cis* correlation between **H**-3, **H**-5 and **H**-6, thus suggesting that the *N*-*t*-Boc group at C-3, and **OH** protons attached C-5 and C-6 are all *cis* to each other. Figure 7.16 illustrates the key  $^1\text{H}$  NMR chemical shifts, 2D NOE correlations and 3D computer model of **7.32**. In addition, the connectivity of C-6 to C-7 was further confirmed by correlations among the respective **H**-6 methine and **H**-7 methylene protons.

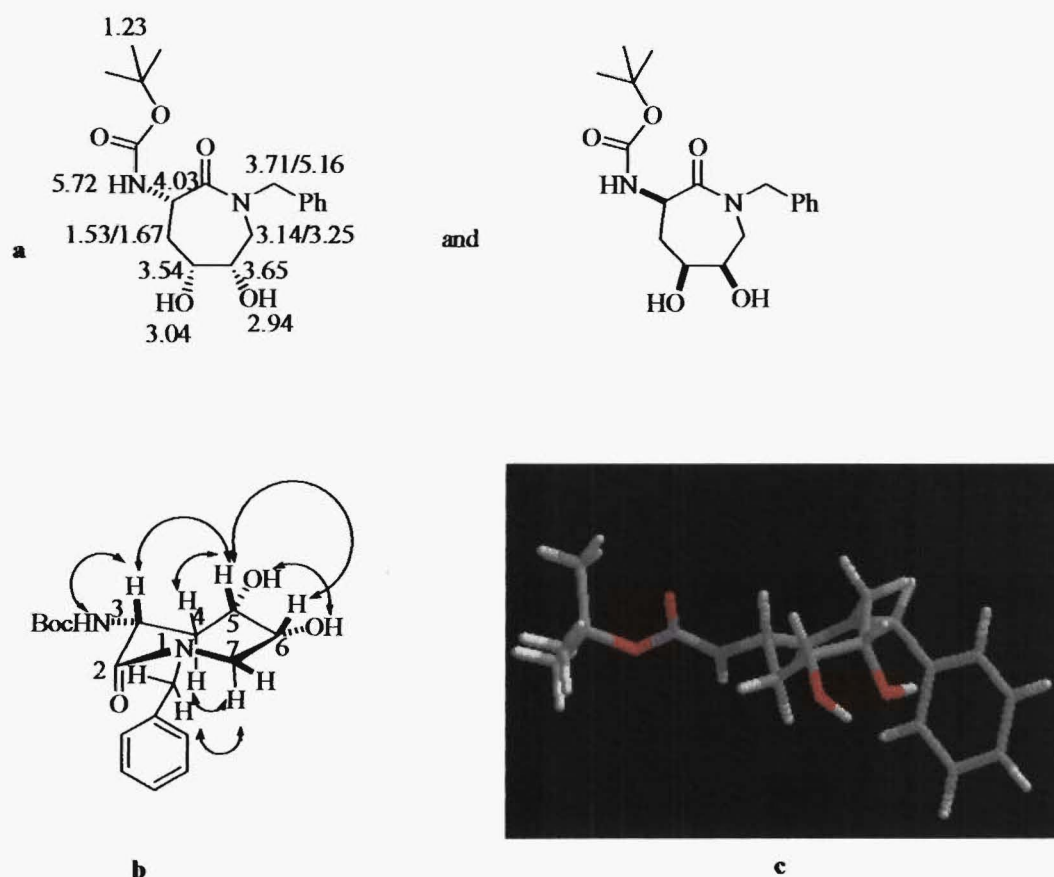
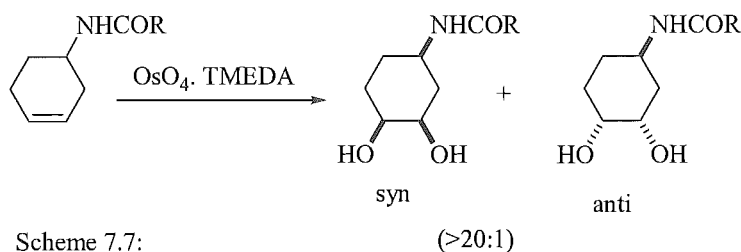


Figure 7.16 a) Key <sup>1</sup>H NMR chemical shifts, b) Key 2D correlations and c) 3D computer model of (±)-7.32.

The structural assignment of the major diol **7.32** suggests that the attack of osmium occurs *syn* to N-*t*-Boc group irrespective of the facial selectivity of chiral ligands. This *syn*-stereoselectivity is proposed<sup>38</sup> as a result of the enhanced hydrogen bonding of the osmate ester intermediate with the nitrogen of the N-*t*-Boc group. Thus, the N-*t*-Boc group acts as a director in the osmium catalyzed dihydroxylation reaction of olefinic lactam **7.30** and the *syn* diol **7.32** is formed in excess (90%) compared to the minor isomer **7.33** (10%). Donohoe *et al.*<sup>38</sup> have reported analogous *syn*-stereoselectivity during their research on the osmium catalyzed *cis* dihydroxylation of six-membered cyclic olefins (see Scheme 7.7).

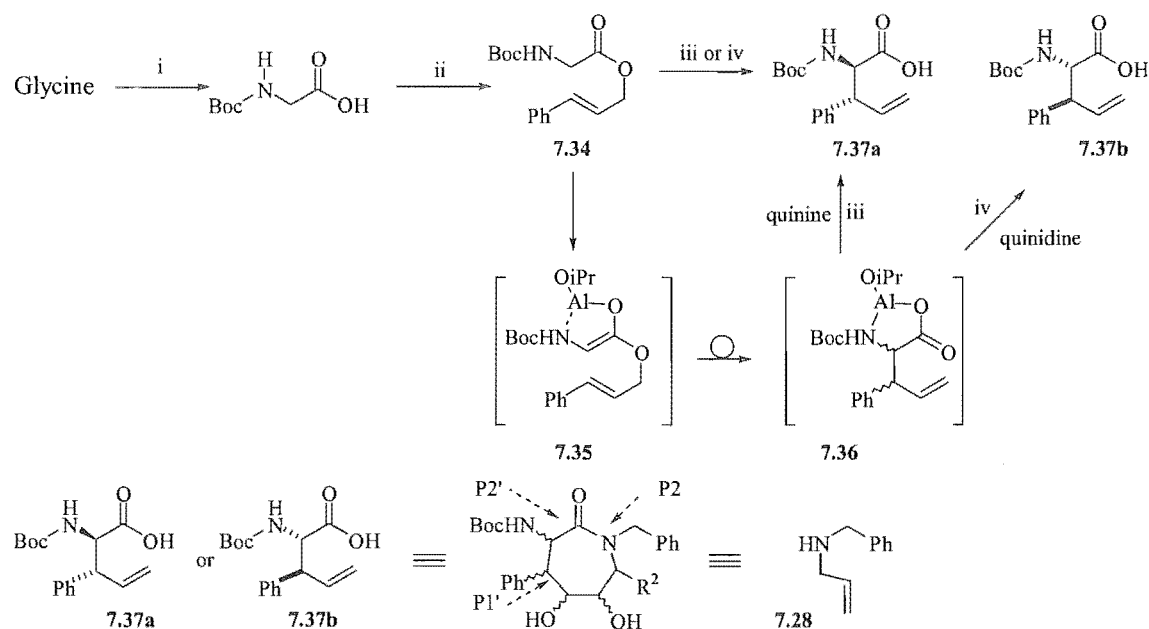


Other literature reports also reveal that substituents containing hetero atoms (S<sup>39</sup>, N, O) in allylic and homoallylic positions direct the course of osmium-catalyzed dihydroxylation.<sup>29a,38,40</sup>

### 7.5 Experiment 2: Stereoselective synthesis of substituted Lactam analogue having P1' = Ph, P1 = H.

Attempts were next directed to the introduce the P1', P2' and P2 substituents into the seven-membered lactam ring (Scheme 7.8). The synthesis<sup>41</sup> of unnatural amino acids **7.37a** and its enantiomer **7.37b** gives rise to the possibility of the introduction of P2' and P1' substituents into the lactam ring in a stereodefined manner (see Scheme 7.8). Synthesis of acids began with Boc protection of the NH<sub>2</sub> group of (±)-glycine using BOC-ON reagent [(2-*ter*-butoxycarbonyloxyimino)-2-phenyl acetonitrile]. (±)-N-*t*-Boc glycine was then coupled to cinnamoyl alcohol in the presence of DCC and DMAP in DCM to give cinnamoyl N-*t*-boc glycinate **7.34** in 92% yield. The Claisen rearrangement of **7.34** in the presence of chiral ligand quinine gave the acid **7.37a** in 50% yield, whereas the same reaction in the presence quinidine (enantiomer of quinine) gave the enantiomer (**7.37b**) of acid **7.37a**. The Claisen rearrangement of **7.34** is thought to occur through a chelate complex **7.35** which rearranges to **7.36** and subsequently give the acids **7.37a** or **7.37b** depending on the chiral ligand (Scheme 7.8).

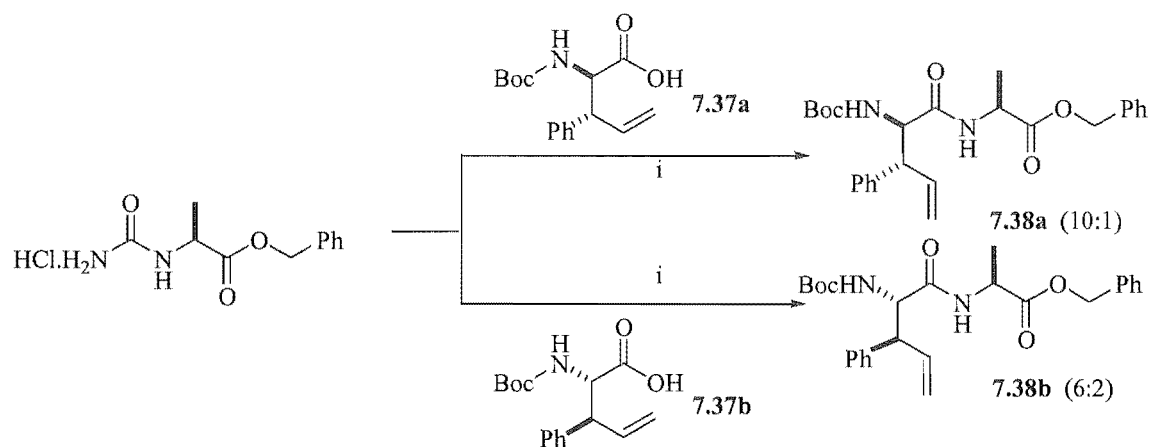




Reagents and conditions: i) BOC-ON, DCM, Dioxane: H<sub>2</sub>O (1:1). ii) Cinnamyl alcohol, DCC, DMAP, DCM  
 iii) Quinine, LHDMS, Al(OiPr)<sub>3</sub>, THF, -78°C to rt. iv) Quinidine, LHDMS, Al(OiPr)<sub>3</sub>, THF, -78°C to rt.

Scheme 7.8: Synthesis of acids **7.37a** and **7.37b**.

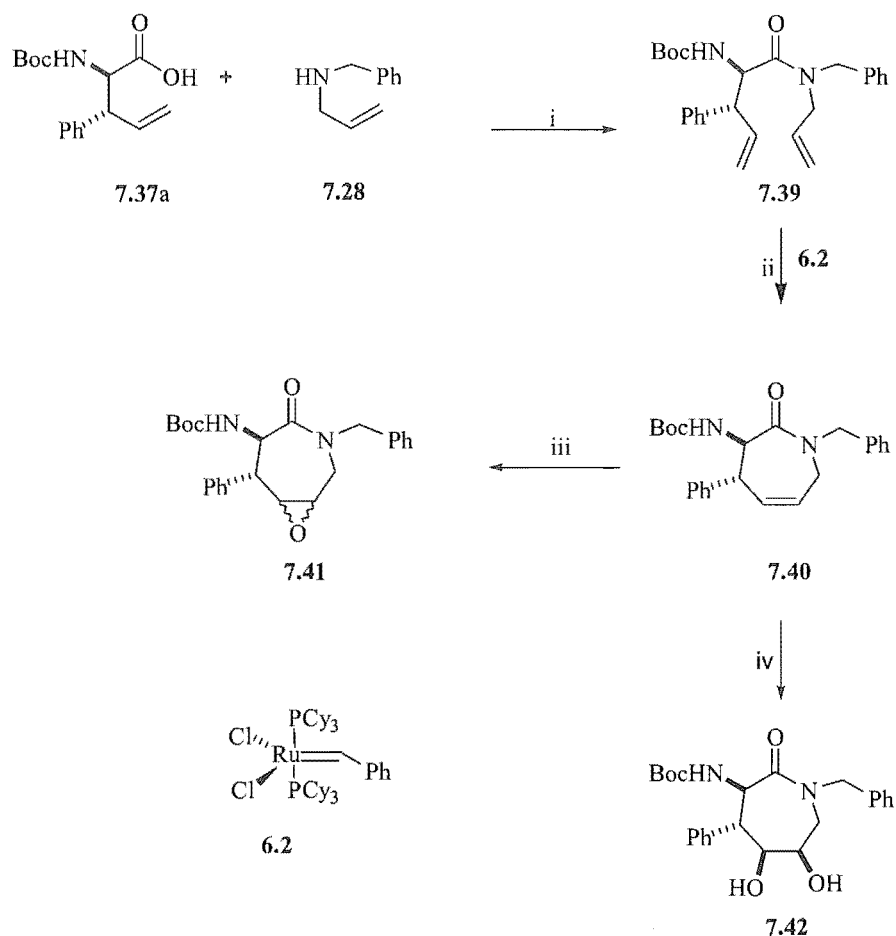
(*S*)-Alanine benzyl ester hydrochloride was coupled separately with both enantiomers of the acid (**7.37a** and **7.37b**) under standard peptide coupling conditions using EDCI, HOBT and NMP (Scheme 7.9), to check if any epimerization had occurred in the Claisen rearrangement of **7.34** (Scheme 7.8, steps iii and iv). Compound **7.38a**, formed from coupling of **7.37a** was obtained as a diastereoisomeric mixture (10:1, based on <sup>1</sup>H NMR, >90% *de*) in 58% yield. In contrast, the amide **7.38b** was obtained as a mixture (6:2, based on analysis of the <sup>1</sup>H NMR spectrum) showing poor diastereoselectivity compared to **7.38a**. Therefore, due to the observed high *de* of the acid **7.37a**, it was chosen for further studies.



Reagents and conditions: i) EDCI, HOBT, NMP, DCM, 16h, rt.

Scheme 7.9: Synthesis of amides **7.38a** and **7.38b**.

The introduction of a P2 substituent (in the form of *N*-benzyl group of the amine **7.28**, see Scheme 7.8) into the seven-membered lactam was allowed by coupling of the acid **7.37a** with *N*-allyl benzyl amine **7.28** under peptide coupling conditions using EDCI, HOBT and NEM to give the precursor for ring-closing metathesis, **7.39** in 44% yield as illustrated in Scheme 7.10.



Reagents and conditions: i) EDCI, HOBT, NEM, DCM, rt, 72 h, 44% ii) Grubb's catalyst **6.2**, DCM, reflux, 24 h, 85% iii) Oxone, acetone, water, 0°C-rt, 87%. iv) (DHQD)<sub>2</sub>PHAL or (DHQ)<sub>2</sub>PHAL, K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>Fe(CN)<sub>6</sub>, MeSO<sub>2</sub>NH<sub>2</sub>, 0°C-rt, 48 h, 51%.

Scheme 7.10: Synthesis of **7.40** and its derivatives **7.41** & **7.42**.

The diene **7.39** was characterized by <sup>1</sup>H and <sup>13</sup>C NMR and was found to be a mixture of two rotamers [(2:1), based on analysis of the <sup>1</sup>H NMR spectrum] as depicted in Figure 7.17. The chemical shift for methine proton attached to phenyl group, and *N*-allylic protons appear as multiplets at δ 3.64-4.20 ppm. The benzylic protons for both isomers appear as doublets between δ 4.27 and 4.68 ppm. The H<sub>α</sub> resonated as triplets at δ 4.87 ppm for major isomer, and δ 4.98 ppm for minor isomer respectively. The olefinic protons resonated as complex multiplets at δ 5.01-6.09 ppm.

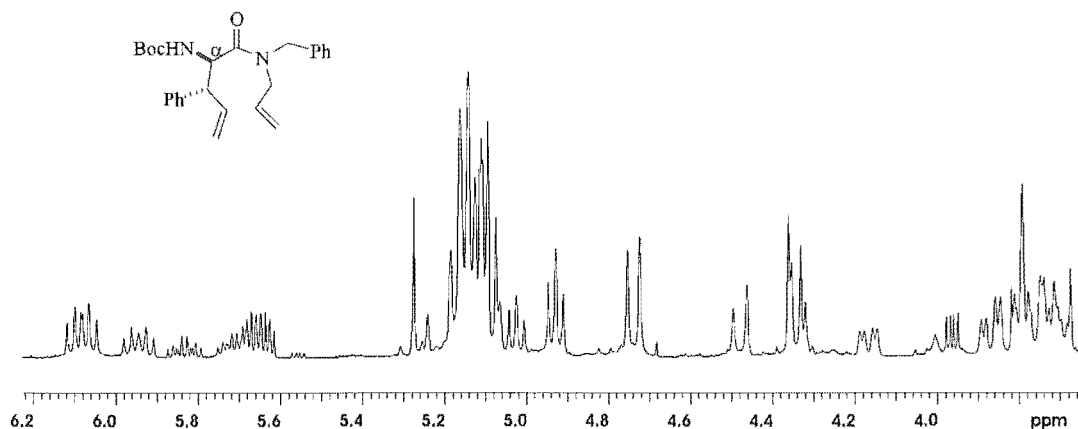


Figure 7.17: Portion of <sup>1</sup>H NMR spectrum of 7.39.

The diene **7.39** was then subjected to ring closing metathesis using Grubb's catalyst (**6.2**) in refluxing DCM under argon atmosphere to give 85% of the lactam **7.40** as a dark brown oil (see Scheme 7.10). After purification of the crude residue by flash column chromatography, the lactam was subjected to <sup>1</sup>H, <sup>13</sup>C, 2D COSY, HSQC/DEPT and mass spectrometry, confirming the compound as **7.40**.

The characteristic <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts and the key 2D COSY connectivity data of **7.40** are illustrated in Figure 7.18. The absence of complex peaks of the olefinic protons of the diene, and the appearance of new peaks for **H-5** and **H-6** olefinic protons at  $\delta$  5.65 and 5.73 respectively, confirmed the formation of the new double bond and ring closure. The key 2D COSY correlations between NH and **H-3** protons established the assignment of the exocyclic resonances, and correlation of **H-4** to **H-3** and **H-5** confirmed connectivity of C-3, C-4 and C-5. The correlation of **H-7** methylene protons with **H-6** established further connection of the seven-membered lactam ring. The structure of the lactam was further confirmed by 2D HSQC/DEPT and high resolution mass spectrometry data which revealed that the observed  $[MH]^+$  for C<sub>24</sub>H<sub>29</sub>N<sub>2</sub>O<sub>3</sub> (393.2204) was in agreement with the calculated one (393.2178).

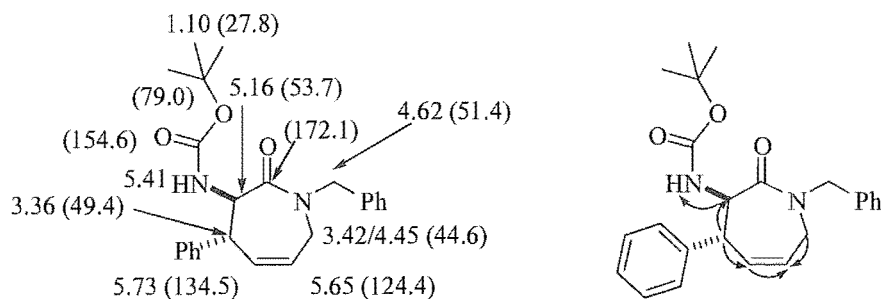


Figure 7.18: a) Key  $^1\text{H}$  and  $^{13}\text{C}$  NMR (in brackets) chemical shifts and b) connectivity data obtained from 2D COSY experiment for **7.40**.

The next step was the derivatization of the double bond of olefinic lactam **7.40**, as for **7.30**. The lactam **7.40** was epoxidized<sup>37</sup> using Oxone® and acetone/water (see Scheme 7.10). The epoxide **7.41** was obtained as a (~ 5:4) mixture of two diastereoisomers (determined by analysis of the  $^1\text{H}$  NMR spectrum) in 87%, which could not be separated by crystallization or column chromatography (Figure 7.19). Therefore, the configuration of the diastereoisomers could not be assigned.

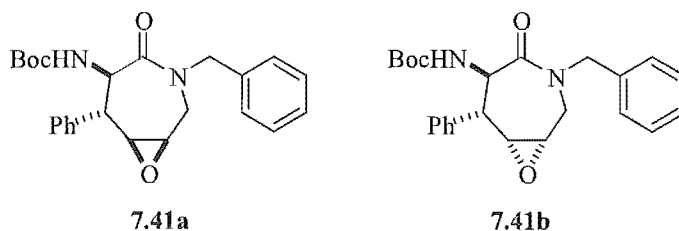
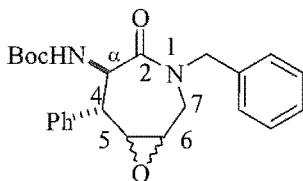


Figure 7.19: Two possible epoxides from the epoxidation of lactam **7.40**.

Table 7.5 summarizes the key  $^1\text{H}$  NMR chemical shifts for **7.41a** and **7.41b**, which shows that H- $\alpha$ , H-4, H-5 and H-7 appear as multiplets for both isomers in the same regions. The NH proton of **7.41a**/or **b** resonated ~0.17 ppm higher field for major isomer compared to the minor isomer. However, the chemical shift for H-4 proton for major isomer resonated

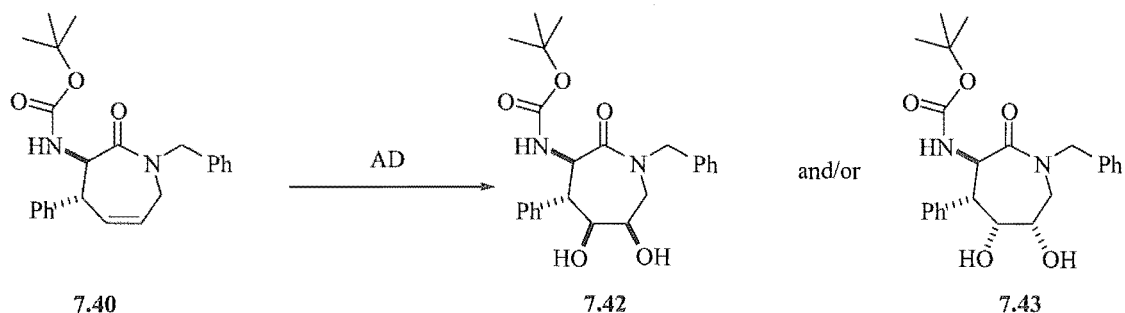
lower field at  $\delta$  3.21-3.28 compared to the chemical shift for the same proton for minor isomer ( $\delta$  3.94).

Table 7.5: Characteristic  $^1\text{H}$  NMR Chemical shifts of a mixture of epoxides **7.41**.



isomer	H-4	H-7	H $_{\alpha}$	H-5	H-6	NH
major	3.21-3.28	3.69-3.76	4.89-4.90	3.21-3.28	3.12-3.18	5.41
minor	3.94	3.69-3.76	4.89-4.90	3.21-3.28	3.00-3.11	5.24

After synthesis of the epoxide derivatives, the lactam **7.40** was subjected to Sharpless AD conditions (see Scheme 7.10, step iv). The AD of lactam **7.40** could give rise to two *syn*-diols **7.42** or **7.43**, formed from the top or bottom attack of  $\text{OsO}_4$  (Scheme 7.11).



Scheme 7.11: Two possible Diastereoisomers **7.42** or **7.43** formed from AD of **7.40**.

The reaction of **7.40** with either ligand **7.21** or **7.22** gave a single diastereoisomer (determined by analysis of  $^1\text{H}$  NMR spectrum), which was assigned structure **7.42** based on a 2D NOE experiment (Figure 7.20), in 51% yield along with 36% of the recovered starting

material **7.40**. The key  $^1\text{H}$  NMR chemical shifts, 2D NOE correlations and a 3D computer model of **7.40** are illustrated in Figure 7.20. The key 2D NOE correlation of **H-4** (Figure 7.20b) with **NH** and **OH** protons at C-5, C-6, establish their *cis*-relationship to each other. Similarly, the 2D correlation between **H-3**, **H-5** methine and **H-7** methylene assigns a *syn* configuration of the *N-t*-Boc group to the **H-5** hydroxyl, and confirms their proximity to **H-7** (Figure 7.20c). Further *syn* relationship of the **H-5** and **H-6** methine protons and **OH** protons was confirmed by 2D NOE correlations between these protons.

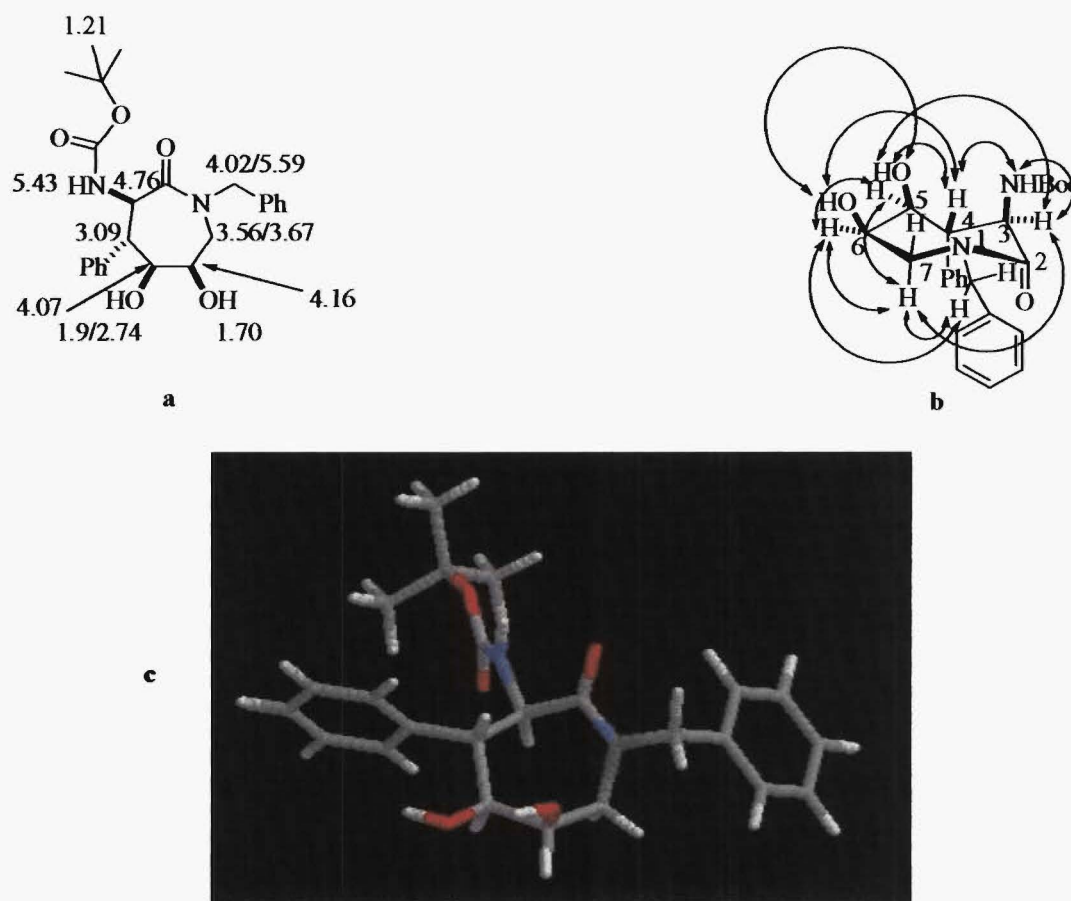


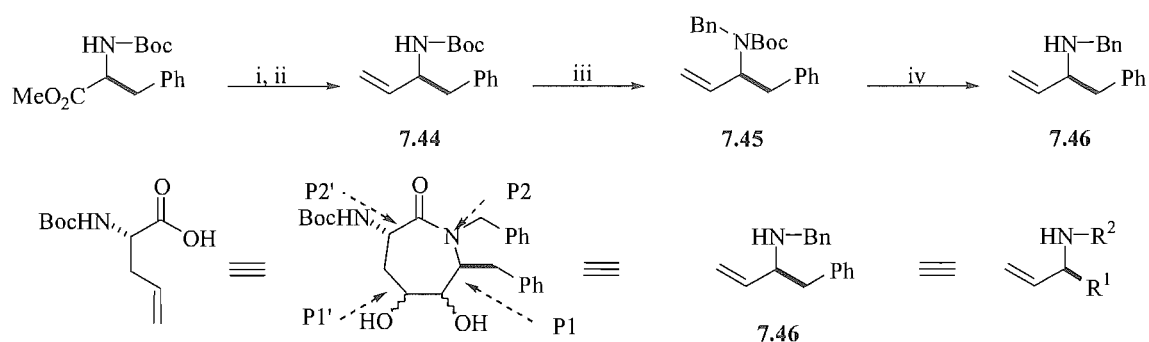
Figure 7.20 a) Key  $^1\text{H}$  NMR chemical shifts, b) Key 2D NOE correlations and c) 3D computer model of **7.42**.

The *syn* configuration of the N-*t*-Boc group to the 5- & 6-OH protons suggests that the *syn*-attack of osmium to N-*t*-Boc group occurs as before (for AD of lactam 7.30), due to enhanced hydrogen bonding<sup>38</sup> of the NH to the intermediate osmate ester, irrespective of the facial selectivity of the chiral ligands 7.21 or 7.22. The *syn*-stereoselectivity of osmium to the N-*t*-Boc group is further reinforced by the (*R*)-stereochemistry of the phenyl group at 4-position which is evident by the generation of a single diastereoisomer 7.42 from lactam 7.40, compared to the synthesis of a (9:1) mixture of diastereoisomers 7.32 & 7.33 from the AD of lactam 7.30 (see section 7.4) that lacks an allylic substituent. Thus, dihydroxylation occurs anti to phenyl group which is the sterically favored face.

### 7.6 Experiment 3: Stereoselective synthesis of substituted Lactam analogue having P1 = Bn, P1' = H.

There is a considerable scope for the introduction of natural amino acid-based P1 and P2 substituents into the seven-membered lactam ring (Scheme 7.12). The preparation of the amine bearing P1 and P2 substituents is achieved by the manipulation of an  $\alpha$ -amino acid, as depicted in Scheme 7.12. The transformation<sup>28</sup> of (*S*)-N-*t*-Boc phenyl alanine into amine 7.46 allows the introduction of a benzyl P1 substituent that mimics the polypeptide substrate of the HIV protease. DIBAL(H) reduction of (*S*)-N-*t*-Boc phenyl alanine methyl ester in dry toluene at -78° C gave the corresponding aldehyde, which was used in next step of Wittig olefination without further purification to give the olefinic amine 7.44 in 45% yield (see Scheme 7.12). Treatment of the 7.44 with NaH and BnBr at 0°C gave the benzylated amine 7.45 in 68% yield, along with 20% of recovered starting amine 7.44, which was treated with TFA in DCM at 0°C to give the desired amine 7.46. The versatility of this method lies in the fact that a variety of amino acid based P1 substituents ( $R^1$ , Scheme 7.12) could be introduced into the seven-membered lactam ring as depicted in Scheme 7.12. In addition, a choice of P2 groups could be introduced by the introduction of different N-protecting groups [ $(R^2)$ , step iv, Scheme 7.12].

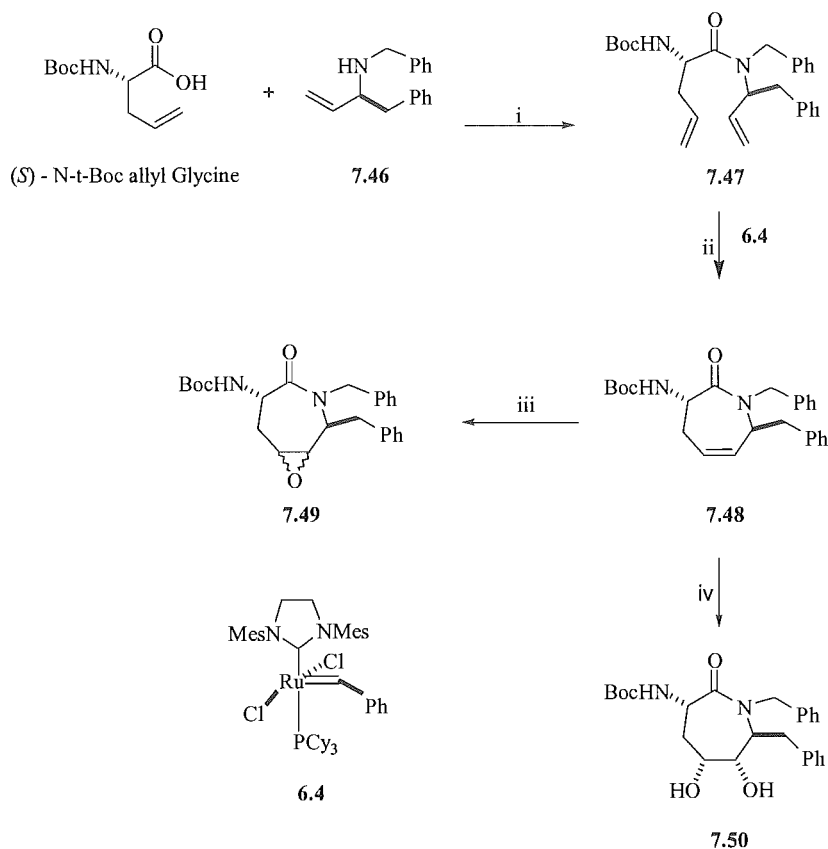




Reagents and conditions: i) DIBAL, Toluene,  $-78^\circ\text{C}$ . ii)  $\text{CH}_3^+\text{PPh}_3\text{Br}^-$ , THF, LiHDMS,  $-78^\circ\text{C}$ -r.t. iii)  $0^\circ\text{C}$ , NaH, BnBr, DMF. iv) TFA, DCM,  $-78^\circ\text{C}$ .

Scheme 7.12: Synthesis of amine **7.46**

Coupling of the amine **7.46** with (*S*)-allyl glycine under standard peptide coupling conditions using EDCI, HOBT and DIPEA could not be achieved probably due to steric crowding of the amine. However, coupling of **7.46** with (*S*)-allyl glycine was accomplished in the presence of BOP coupling reagent and DIPEA by stirring the reaction mixture at rt for 48 h in dry DCM to give the diene **7.47** in 67% yield (Scheme 7.13). The progress of the coupling reaction was monitored by TLC, and the turnover of the reaction was increased by the addition of another four equivalents of BOP in portions to the reaction mixture.<sup>42</sup> Scheme 7.13 depicts the synthetic steps involved in the synthesis of **7.47**, **7.48**, **7.49**, and **7.50**.



Reagents and conditions: i) BOP, DIPEA, DCM, rt, 72h, 67%. ii) Grubb's catalyst **6.4**, DCM, reflux, 36h, 92% iii) Oxone, acetone, water, rt, 84%. iv) (DHQD)<sub>2</sub>PHAL or (DHQ)<sub>2</sub>PHAL, K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>Fe(CN)<sub>6</sub>, MeSO<sub>2</sub>NH<sub>2</sub>, 0°C-rt, 48h, .52-65 %

Scheme 7.13: Synthesis of **7.48** and its derivatives **7.49** & **7.50**.

The complex <sup>1</sup>H NMR spectrum (Figure 7.21) of **7.47** showed the presence of a rotameric mixture (3:2, determined by analysis of the <sup>1</sup>H NMR spectrum) at rt. The allylic protons next to H<sub>α</sub>, and benzylic protons attached to methine proton appear as multiplets at δ 2.84-3.01 ppm. The methine H adjacent to benzylic methylene protons, and N-CH<sub>2</sub> protons resonate between δ 4.26 and 4.83 ppm for both isomers.

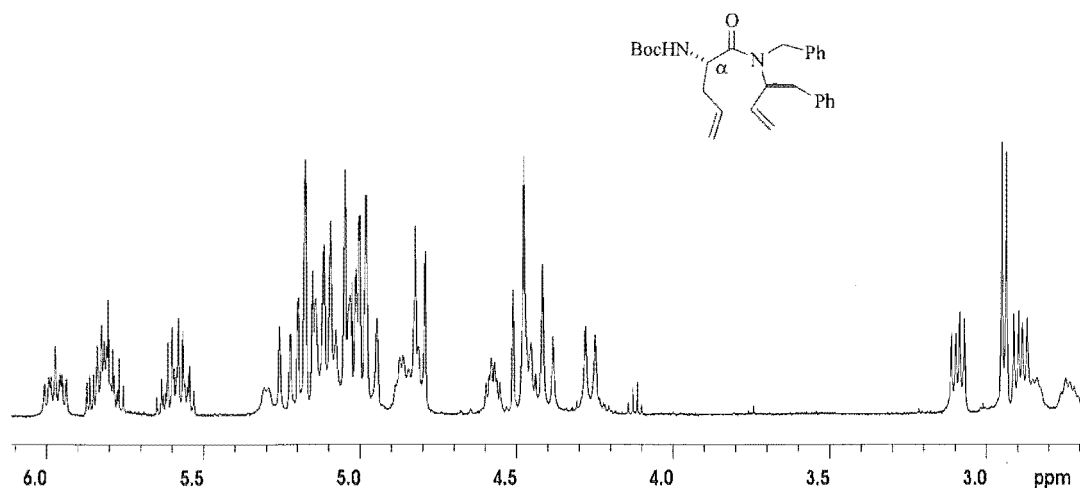


Figure 7.21: Portion of the  $^1\text{H}$  NMR spectrum of **7.47**.

The  $\text{H}_\alpha$  for both isomers resonated as multiplets at  $\delta$  4.85-4.87 ppm. Further complex pattern of olefinic protons at  $\delta$  4.95-6.01 confirmed the presence of two rotamers at rt. The presence of the two isomers was further established by the  $^{13}\text{C}$  NMR spectrum which showed double characteristic resonances for all carbons. Further confirmation of **7.47** was made by the observed  $[\text{MH}]^+ \text{C}_{27}\text{H}_{35}\text{N}_2\text{O}_3$  (435.2635), which was found to be in agreement with the calculated mass (435.2648).

Ring closing metathesis of the diene **7.47** was achieved using Grubb's catalyst (**6.4**) in refluxing DCM to give 92% of the olefinic lactam **7.48** (Scheme 7.13, step ii). The key  $^1\text{H}$  NMR and 2D COSY connectivity data for **7.48** are illustrated in Figure 7.22. The characteristic chemical shifts for **H-5** and **H-6** olefinic protons are observed at  $\delta$  5.77 and 5.46 ppm respectively, confirming the formation of a new double bond. The key 2D correlations among NH,  $\text{CH}_\alpha$ , **H-4** methylene and **H-5** olefinic protons established connectivity of C-5 to C4 and C-3 and exocyclic N-*t*-Boc group in **7.48**. Similarly, 2D correlations between **H-6** and **H-7**, and **H-7** and the benzylic protons further confirm the structure of **7.48**.

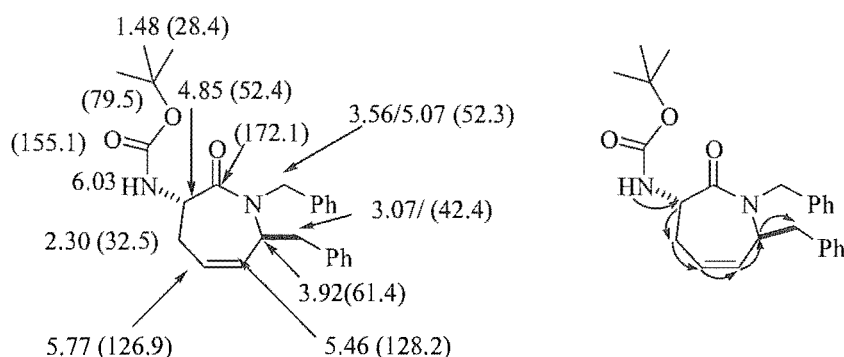


Figure 7.22: a) Key  $^1\text{H}$  and  $^{13}\text{C}$  NMR (in brackets) chemical shifts and b) connectivity data obtained from 2D COSY experiment for **7.47**.

Further confirmation of the structure of **7.48** was done by high resolution mass data; which revealed the value for  $[\text{MH}]^+$  to be 429.2157, whereas the calculated value for  $[\text{MH}]^+$  is equal to 429.2154.

Functionalization of the double bond of lactam **7.48** via epoxidation (as before for **7.30** and **7.40**) was carried out using Oxone® and acetone/water (see Scheme 7.13, step iii) to give the epoxide **7.49** as a mixture (~1:1, determined by analysis of the  $^1\text{H}$  NMR spectrum) of two diastereoisomers in 84% (Figure 7.23), which could not be separated by column chromatography or crystallization.

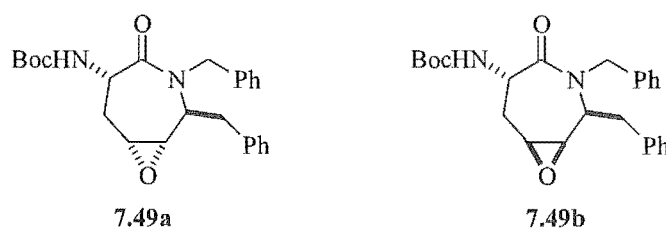
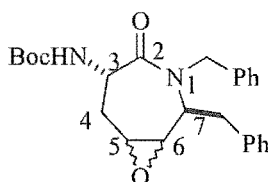


Figure 7.23: Two diastereoisomers formed from the epoxidation of lactam **7.48**.

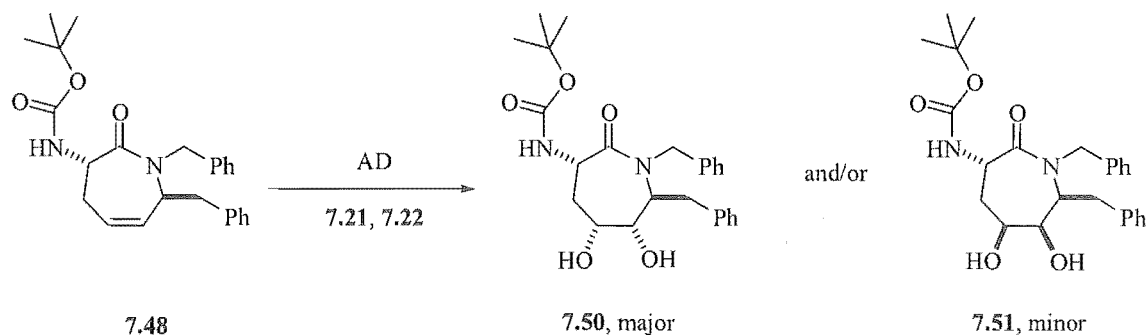
Table 7.6 summarizes the characteristic  $^1\text{H}$  NMR chemical shifts for **7.49a/b**. An analysis of the chemical shifts for the two isomers reveal that the protons for one isomer resonated higher field compared to the other isomer.

Table 7.6: Characteristic  $^1\text{H}$  NMR Chemical shifts of a mixture of epoxides **7.49a-b**.



isomer	$\text{H}_\alpha$	$\text{H-4}$	$\text{H-5}$	$\text{H-6}$	$\text{H-7}$	NH
<b>7.49a/ or b</b>	4.55	2.01/2.55	3.11	2.98	3.92	5.79
<b>7.49a/ or b</b>	4.62	2.09/2.69	3.17	3.27	4.11	5.97

Further functionalization of the olefinic lactam **7.48** was then carried out via Sharpless AD using either ligand dihydroquinidine phthalazine [(DHQD)<sub>2</sub>-PHAL] **7.21** or dihydroquinine phthalazine [(DHQ)<sub>2</sub>-PHAL] **7.22** (Scheme 7.14). The AD reaction could occur from bottom or top face to give diastereoisomer **7.50** and /or **7.51** (Scheme 7.14). A single diastereoisomer (determined by analysis of the  $^1\text{H}$  NMR spectrum), was obtained in ~52-60%. The configuration of the diol was assigned based on a 2DNOE experiment, confirming **7.50** as the structure of the diol.



Scheme 7.14: Two possible Diastereoisomers **7.50** or **7.51** from AD of **7.48**.

The key  $^1\text{H}$  NMR chemical shifts, connectivity data obtained from 2D NOESY studies, and 3D computer model of **7.50** are depicted in Figure 7.24.

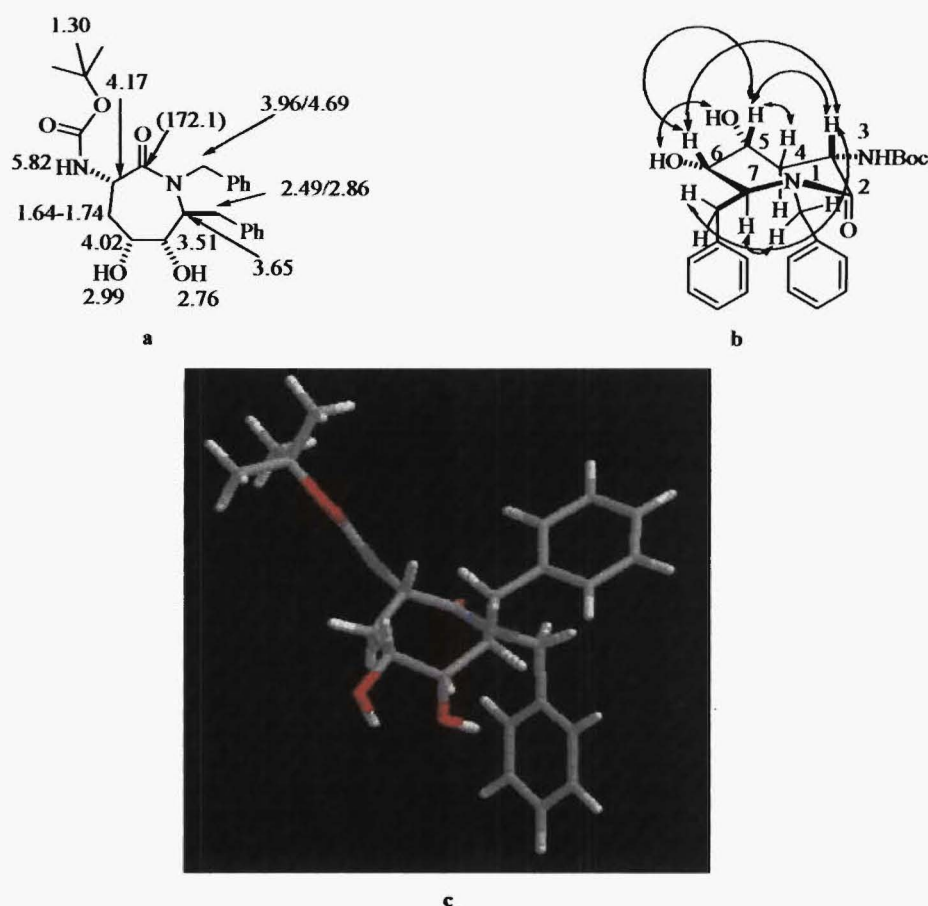


Figure 7.24: a) Key  $^1\text{H}$  chemical shifts, b) connectivity data obtained from 2D NOESY and c) computer model of **7.50**.

The 3-*N*-*t*-Boc group has the same relative configuration, but opposite absolute configuration as the 7-benzyl group in **7.50**. The absolute configuration at 3 and 7 positions came over from the starting substrates and was confirmed from the 2D NOE data. The *cis* relationship of the 5 and 6-OH protons with the *N*-*t*-Boc group was established by the 2D NOE correlations among **H-3**, **H-5** and **H-6** methine protons. The correlation between **H-7** and the neighbouring **H-6** methine proton confirms their connectivity. The correlation of

benzylic CH<sub>2</sub> (attached to C-7) with H-5 and H-3 methine, and *N*-benzyl protons suggest their proximity in space (Figure 7.24 c). The structural assignments of the diol **7.50**, therefore, suggest that the attack of osmium has occurred *syn* to *N*-Boc group (as before for **7.30** and **7.40**) and anti to the (*S*)-benzyl group of lactam **7.48**. Thus, the 7-benzyl group enhances the *syn*-stereoselectivity of the *N*-*t*-Boc group in the AD of **7.48**, by generating a single diastereoisomer **7.50**, compared to the synthesis of a mixture (9:1) of diols (**7.32** and **7.33**) from lactam **7.30**, that lacks a substituent at 4 or 7 position.

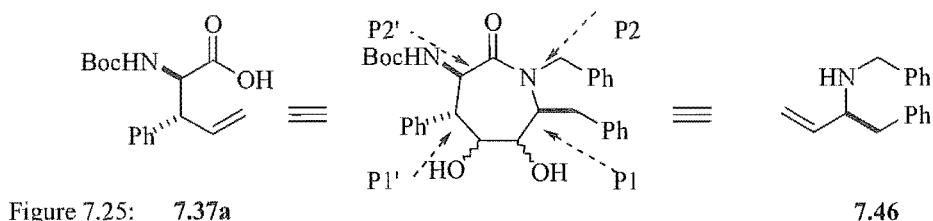
*Cis*-dihydroxylation of **7.48** in the absence of ligands was also carried out to check the role of (*S*)-benzyl group and ligands; and was anticipated to proceed on the sterically less hindered face, anti to benzyl group (Scheme 7.14). Experimentally, the *cis*-diol **7.50** was obtained as a single isomer (based on <sup>1</sup>H NMR). The generation of a single diastereoisomer **7.50** (determined by <sup>1</sup>H NMR) in the presence or absence of ligands, strongly suggests that it is the carbamate group of **7.48** which directs the course of dihydroxylation; and that the 7-(*S*)-configured benzyl group further enhances the *syn*-directing effect of the carbamate group.

In the light of results obtained from experiments 1-3, it is concluded that the attack of osmium is always preferred *syn* to the carbamate group (in the dihydroxylation of **7.30**, **7.40** and **7.48**), and the stereochemistry of (*R*)-4-phenyl group (**7.40**) and (*S*)-7-benzyl group (**7.48**) further reinforce the *syn*-selectivity of the carbamate group in the AD reaction.

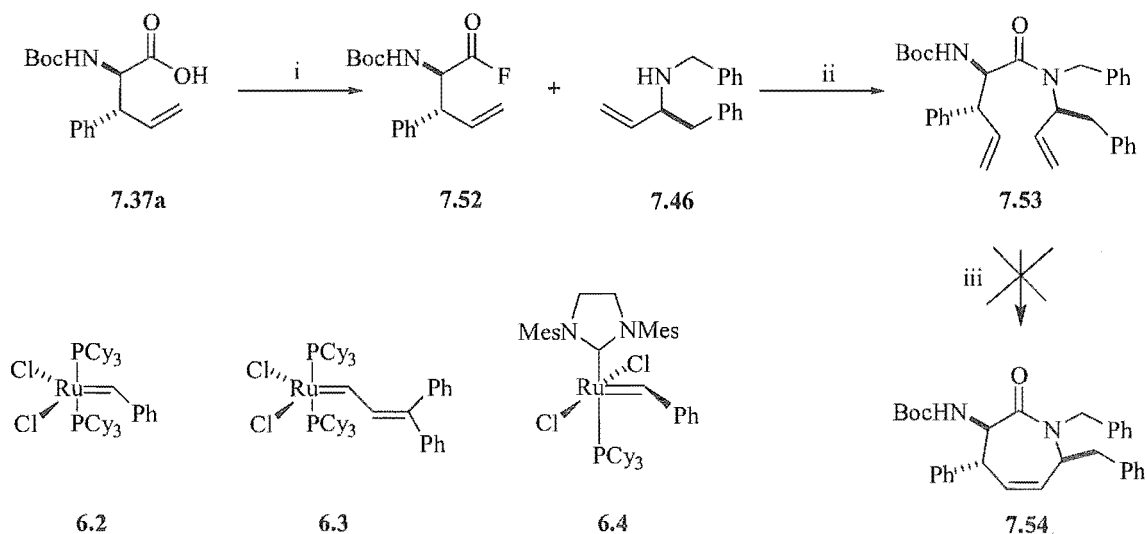
## 7.7 Experiment 4: Stereoselective synthesis of substituted Lactam analogue having P1 = Bn, P1' = Ph.

De Lucca *et al.*<sup>26</sup> reported the presence of all P1, P2, P1' and P2' substituent (see Figure 7.9) as a requirement for optimum potency of a lactam-based HIV protease inhibitor.

Efforts were made to introduce the P1, P2, P1' and P2' substituents into the seven-membered lactam ring, by coupling of the acid **7.37a** with the amine **7.46** (see Figure 7.25).



Attempts to couple the acid **7.37a** with amine **7.46** using conventional peptide coupling reagents e.g. EDCI, DCC or BOP failed, probably because of the steric crowding of both acid **7.37a** and amine **7.46**. Coupling was however, achieved by first transforming the acid **7.37a** to the corresponding acid fluoride **7.52** by reacting it with pyridine and cyanuric fluoride.<sup>43</sup> The crude acid fluoride **7.52** was coupled with the amine **7.46** in the presence of DIPEA to give the diene **7.53** in 12% yield (Scheme 7.15).



Reagents and conditions: i) pyridine, Cyanuric fluoride, DCM. ii) DIPEA, DCM.

iii) **6.2/ 6.3/ and 6.4.**

Scheme 7.15: Attempted synthesis of the lactam **7.54**.



The crude residue was purified by column chromatography. The complexity of  $^1\text{H}$  NMR of **7.53** revealed that the diene was a mixture of rotamers. Ring closing metathesis of **7.53** was attempted using Grubb's catalyst **6.2**, **6.4** and extended chain catalyst **6.3**. However, the ring closure could not be achieved using any of the above mentioned catalysts, and starting material **7.53** was recovered in each case. This could be due to the blockage of the catalytic cycle of RCM by the presence of steric bulk near the olefinic chains. The blockage of the catalytic cycle of RCM by increased substitution in the proximity of the double bonds has also been reported in the literature.<sup>44</sup>

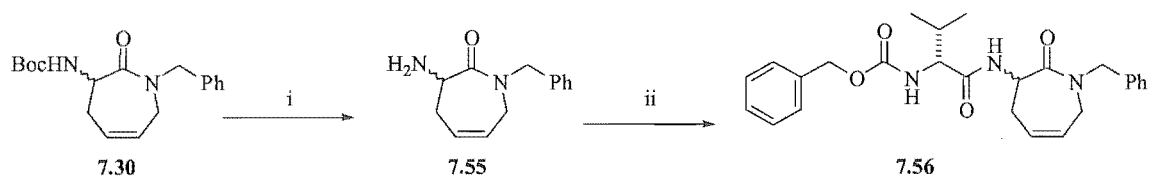
Unfortunately, the synthesis of the ideal target HIV protease inhibitor containing all P1, P2, P1' and P2' substituents (Figure 7.25) was unsuccessful using this methodology. Recent advancement in ring closing metathesis by using microwave radiation<sup>45</sup> has made possible the ring closing reaction of substrates that were not possible, or very slow without microwave radiation. Research will be focused on the ring closing metathesis of **7.53** using microwave radiation as well as other more powerful RCM catalysts in the near future, to get the desired tetra substituted seven-membered HIV protease inhibitors. What follows is a brief introduction of the six-membered lactams and their attempted synthesis during the course of this research work.

## **7.8 Extension of the N-Terminus of the Seven-Membered Cyclic Lactam**

### **7.30**

Studies<sup>11</sup> have shown that one of the requirement for a potent HIV protease inhibitor is the introduction of groups capable of forming hydrogen bonds in the active site of the HIV protease. Extension of the  $\text{NH}_2$  terminus of the lactam by removing Boc group and coupling of the resulting free amine to another amino acid would lead to the possibility of introducing amino acid residues into the lactam inhibitor to increase the hydrogen bonding interactions of the inhibitor in the active site of the enzyme. The removal of Boc group

from olefinic lactam **7.30** was thus achieved by stirring the lactam with 1N HCl (aq) in ethyl acetate for 4h at rt to give the free amine **7.55** in 100% as depicted in Scheme 7.16. The crude amine **7.55** was then coupled with N-Cbz-(*S*)-Valine in the presence of EDCI, HOBT and DIPEA to give a diastereomeric mixture (~ 1:1, determined by  $^1\text{H}$  NMR) of the resulting amide **7.56** in 68% yield.



Reagents and conditions: i) 1N HCl (aq.), EA, rt, 4h, 100%. ii) N-Cbz- (*S*)-Valine, EDCI, HOBT, DIPEA, rt, 16h, 68%.

Scheme 7.16: Synthesis of the amide **7.56**.

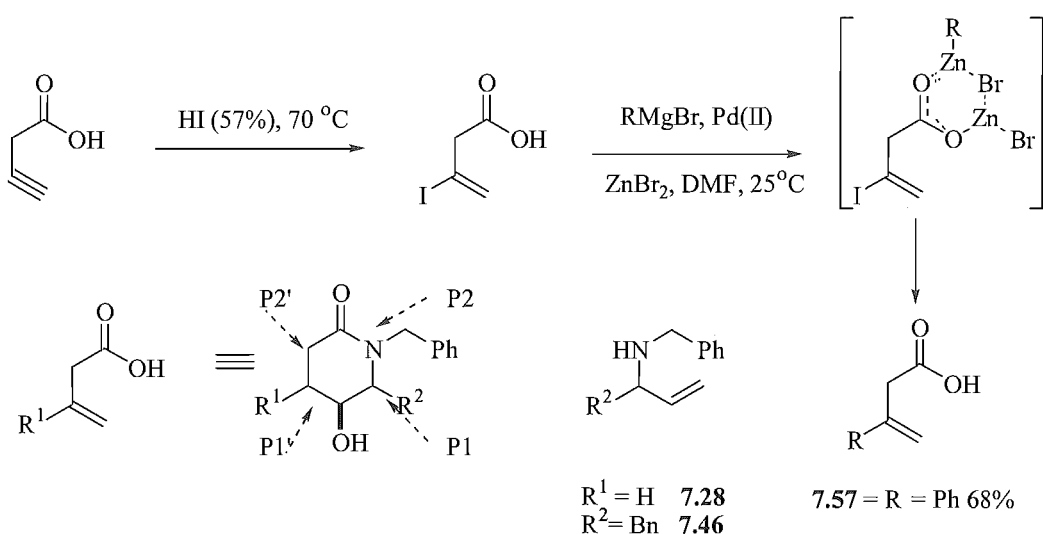
Further derivatization of the double bond of the lactam **7.56** via epoxidation and dihydroxylation could not be carried out due to lack of time. However, research work in future will be focused on functionalization of the double bonds of extended chain inhibitors (e.g. **7.56**).

## 7.9 Synthesis of Six-membered $\delta$ -lactams using Ring-Closing Metathesis Methodology

Various<sup>26, 27, 28</sup> synthetic procedures have been applied to the synthesis of six-membered lactam inhibitors as discussed earlier in section 7.1. Previous research in our laboratories,<sup>28</sup> has also led to the synthesis of six-membered lactam analogue lacking a P1' substituent (Scheme 1.6, Chapter 1). The lack of a P1' substituent (as depicted in Figure 7.9) has been reported to be the probable cause of the loss in antiviral potency, of the six-membered lactams and related six-membered cyclic urea-based HIV protease inhibitors.<sup>26</sup> Research was thus focused on the synthesis of six membered ring lactams containing the missing P1'

substituent as depicted in Scheme 7.17. What follows is a discussion about the attempted synthesis of six membered ring lactams.

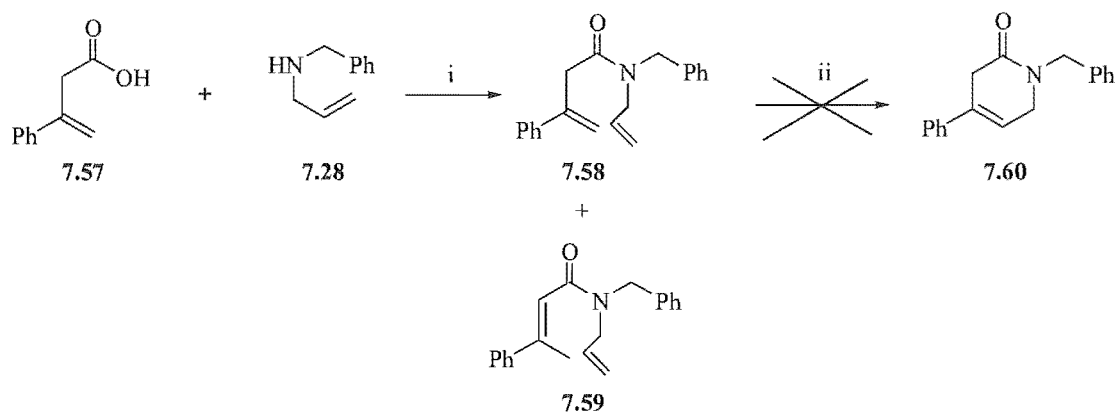
The introduction of a P1' substituent into the target six-membered lactam was achieved by the synthesis<sup>46</sup> of 3-phenyl but-3-enoic acid **7.57** using literature method (Scheme 7.17). Iodo-3-butenic acid was synthesized by treating 3-butenic acid with HI at 70 °C. Coupling of the iodo-3-butenic acid with phenyl zinc bromide (generated by the addition of zinc bromide to phenyl magnesium bromide in dry ether) in the presence of 5% PdCl<sub>2</sub>(MeCN)<sub>2</sub> in dry DMF gave the respective acid **7.57** in 68% yield (Scheme 7.17).



Scheme 7.17: Synthesis of 3-substituted butenoic acid **7.57**.

The synthetic plan involved was to couple the acid first with simple *N*-allyl benzyl amine, and carry out the RCM. The next step would involve coupling of the acid to the amino acid derived amine **7.46** to introduce both P1 and P2 substituents into the six-membered lactam ring (Scheme 7.17).

The introduction of a P2 substituent into the six-membered lactam was managed by coupling of the acid **7.57** with *N*-allyl benzyl amine **7.28** in the presence of EDCI, HOBT and DIPEA to give the diene **7.58**, along with the by-product **7.59** formed from isomerisation of the terminal double bond. RCM of the diene **7.58** was attempted using a number of reaction conditions (including carrying out the reaction in the presence of Grubb's catalysts **6.2**, or **6.4**, at rt as well as at reflux, in dry degassed DCM, benzene or toluene) as shown in Scheme 7.18. But the reaction was unsuccessful under all these conditions.



Conditions: i) EDCI, HOBT, NMP, DMF, rt. ii) Grubb's catalysts **6.2**, **6.4**, DCM (Benzene, or toluene), rt or reflux.

Scheme 7.18: Attempted synthesis of six-membered ring lactam

Due to failure of the RCM of the terminally substituted diene **7.58**, further work was stopped at this stage. However, future work could involve extension of this work as discussed in the next section.

## 7.10 Conclusion and Future Work

In summary, a versatile and general method for the synthesis of seven-membered ring lactams using transition metal catalysts has been developed. These lactams have been derivatized to *cis*-diols using Sharpless asymmetric dihydroxylation, and to epoxides. The

*syn*-stereoselectivity of the *tert*-butoxy carbonyl group and its enhancement by allylic substituents with suitable stereochemistry, in osmium catalyzed dihydroxylation reaction has been determined. This has further been confirmed by the generation of a single diastereoisomer (7.50) from the Sharpless AD of the 7-benzyl substituted lactam (7.48) in the absence of ligands (7.21 and 7.22). The synthesized *cis*-diols will be sent for testing their biological activity against HIV. Extension of the amino terminus of the seven-membered lactam (7.30) has also been successfully achieved, which determine the considerable scope of the introduction of amino acid residues capable of increasing the H-bonding interaction in the active site of the HIV protease, required for enhancement in potency of such inhibitors.

Future work in this area could involve optimizing the conditions for the synthesis of the six and seven-membered lactam analogues of HIV protease inhibitors using ring-closing metathesis methodology. Optimization could involve microwave-assisted RCM for the synthesis of tetra-substituted six and seven-membered lactam-based HIV protease inhibitors. Further research could also include ring closing metathesis in the presence of new and improved catalysts to synthesize the desired tetrasubstituted six- and 7-membered lactam inhibitors and their derivatives, which could prove potent and selective HIV protease inhibitors. Future work could also involve, extension of the seven-membered *cis*-diol mimetics and coupling with other amino acids.

## 7.11 References for Chapter Seven

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**CHAPTER EIGHT**  
**EXPERIMENTAL**

## 8.1 General Methods

### Nuclear Magnetic Resonance<sup>1</sup>

<sup>1</sup>H-NMR spectra were recorded on a Varian Inova spectrometer (500 MHz) or a Varian Unity 300 (300 MHz), and <sup>13</sup>C-NMR spectra on a Varian Unity 300 (75 MHz) at 23 °C. Chemical shifts are reported in parts per million (ppm) on the  $\delta$  scale. All spectra were recorded in CDCl<sub>3</sub> using TMS (for <sup>1</sup>H:  $\delta$  = 0) and CDCl<sub>3</sub> (for <sup>13</sup>C:  $\delta$  = 77.0) as internal standard unless otherwise specified. 2D-NMR experiments including COSY, HSQC, NOESY, HMBC were recorded on Varian Inova spectrometer (500 MHz) with a delay (D<sub>1</sub>) of 1s.

### Mass Spectrometry<sup>1</sup>

Electron Impact (EI) mass spectra were detected on a Kratos MS 80 RFA mass spectrometer operating at 4000 V (accelerating potential), 70 eV (ionization energy) and 200-250 °C. Electrospray ionization (ESI) mass spectra were detected on a micromass LCT TOF mass spectrometer, having a probe voltage of 3200 V, temperature of 150 °C and a source temperature of 80 °C. Direct ionization used 10  $\mu$ L of a 10  $\mu$ g mL<sup>-1</sup> solution using a carrier solvent of 50% acetonitrile/H<sub>2</sub>O at a flow rate of 20  $\mu$ L min<sup>-1</sup>. Ionization was aided by the addition of 0.5% formic acid.

### Microanalysis<sup>1</sup>

Microanalysis was performed at the University of Otago Microanalytical Laboratory. All reported values are within the range of  $\pm 0.4\%$  of the calculated value.

### Infrared Spectroscopy<sup>1</sup>

IR spectra were recorded on a Shimadzu 8201PC series FTIR interfaced with an Intel 486 PC operating Shimadzu's Hyper IR software. Spectra were obtained neat on either a KBr disc, in solid KBr or in solution in  $\text{CHCl}_3$ .

### Optical Rotations

Optical Rotations were measured on a Perkin Elmer Polarimeter Model 341, with a 10 mm path length. The  $[\alpha]_D^{20}$  values are reported in units  $\text{deg cm}^2 \text{g}^{-1}$ , with concentrations given in  $10^{-1} \text{g cm}^{-3}$ .

### Reagents and Solvents

All reactions were performed in oven-, or flame-dried glass equipment under an atmosphere of argon, unless otherwise mentioned. All reagents and starting materials were obtained from commercial sources, or otherwise prepared in the laboratory. Analytical thin layer chromatography was performed on glass- or aluminium-backed Merck Kieselgel KG60F<sub>254</sub> silica plates, and visualized using short-wave UV light,  $\text{KMnO}_4$  or phosphomolybdate dip (and dried with a flame). Flash column chromatography was performed on silica gel (Merck Silica gel 60, and Kanto Chemical Co., Inc) following the procedure given by Still and co-workers.<sup>2</sup> EA and petroleum-ether (hexanes) were distilled from  $\text{CaH}_2$  prior to use in chromatography. *N,N*-Dimethylformamide (DMF) was distilled under reduced pressure from  $\text{P}_2\text{O}_5$  initially and then from  $\text{CaH}_2$ , and stored over molecular sieves 4Å under an argon atmosphere. THF,  $\text{Et}_2\text{O}$  and PhH were distilled from sodium benzophenone ketyl immediately prior to use. TEA, DCM and toluene were distilled from  $\text{CaH}_2$  immediately before use, and/or stored over molecular sieves 4Å.  $\text{Pd}(\text{PPh}_3)_4$  was prepared by the literature procedure<sup>3</sup> and all other Pd catalysts and phosphine reagents were obtained from commercial sources. Metathesis catalyst were obtained from Strem

Chemicals. Pentafluorobenzoyl chloride, was used without purification. LDA was prepared from *n*-BuLi and *N,N*-diisopropylamine (distilled from CaH<sub>2</sub>). Grignard's reagents were prepared in the laboratory. All other reagents used in the work described in this thesis were purified according to literature procedures.<sup>4</sup>

## 8.2 General Procedures

### General Procedure A: Preparation of the Di- and trienyl Ketones

The ketone *N,N*-dimethyl hydrazone (1.5 equiv) was treated with freshly prepared LDA (1.5 equiv) [from *n*-BuLi and *N,N*-diisopropylamine in THF (25 mL)] at 0 °C and stirred for 1 h under argon atmosphere. The reaction mixture was then cooled to -78 °C and the dienyl bromide<sup>5</sup> **3.14a** (1 equiv) in THF was added slowly. The reaction was stirred continuously, warmed to rt overnight and quenched by adding aqueous sat. NH<sub>4</sub>Cl solution. The reaction mixture was then extracted with diethyl ether (×3). The combined organic fractions were washed with water, brine, dried over anhydrous MgSO<sub>4</sub> and evaporated in vacuo to give crude the alkylated hydrazone which was used in the next step without further purification.

To a mixture of acetic acid (5 equiv), sodium acetate (1 equiv), water (2 equiv), and THF (2 equiv) was added the crude alkylated hydrazone,<sup>6</sup> and the mixture was stirred at rt for three hours. The reaction was quenched by adding aqueous NaOH solution at 0 °C and the mixture was extracted with ether (×3). The combined organic extracts were washed with water, brine, dried over anhydrous MgSO<sub>4</sub> and evaporated in vacuo. The crude product was purified by flash column chromatography [H/EA = 95/5-90/10] to give the pure dienyl ketone.

**General Procedure B: Preparation of Oxime Derivatives**

The dienyl ketone (1 equiv), hydroxylamine hydrochloride (1.3 equiv) and pyridine (1.5 equiv) were stirred in EtOH (30 mL) at rt for 1 h. The reaction mixture was quenched by adding H<sub>2</sub>O, brine and then 2 M HCl (aq.) and extracted with ethyl acetate. The combined organic fractions were washed successively with 2 M HCl, sat. NaHCO<sub>3</sub> (aq), brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to give a (*E/Z*) mixture of the oximes. The residue was purified by flash column chromatography to give the corresponding oxime.

**General Procedure C: Preparation of *O*-pentafluorobenzoyl Oxime Derivatives**

To a solution of the dienyl ketone oxime (1 equiv) and TEA (1.9 equiv) in DCM (20 ml) at 0 °C was added C<sub>6</sub>F<sub>5</sub>COCl (1.3 equiv) in DCM (5 ml) and stirred for 30 min to 1 h at that temperature. The reaction was quenched by adding H<sub>2</sub>O at 0 °C and extracted with ether (×3). The combined organic extracts were washed with water, brine, dried over anhydrous MgSO<sub>4</sub> and evaporated in vacuo. The crude product was purified by flash column chromatography (H/EA = 95/5) to give the pure dienyl oxime pentafluorobenzoate.

**General Procedure D: Preparation of Spirocyclic Imines by Domino A-H Reaction<sup>7</sup>**

Pd(PPh<sub>3</sub>)<sub>4</sub> (0.01 equiv) was added to a mixture of the *O*-pentafluorobenzoyl oxime (1 equiv), TEA (5 equiv) and molecular sieves 4Å (150 mg) in dry DMF (0.05 M) under argon atmosphere at rt. The reaction mixture was warmed to 110 °C and stirred for 30 min. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to rt, quenched by adding water and extracted with Et<sub>2</sub>O (×3). The combined extracts were washed with water, then brine (×2), dried over anhydrous MgSO<sub>4</sub>, and evaporated in vacuo. The residue was purified by flash column chromatography to give the desired spiroimine.

**General Procedure E: Preparation of Amidoximes**

To a solution of the oxime (1.0 equiv) in dry DMF (25 mL), was added *N*-chlorosuccinimide (1.01 equiv) in portions. The reaction mixture was heated to 50-70 °C and stirred for 2 h. The reaction mixture was then cooled to rt, and a solution of *N*-allyl benzyl amine<sup>8</sup> (1.2 equiv) in DMF (5 mL) was added to the reaction mixture and stirring was continued for 2-4 h (monitored by TLC) at 70 °C. The mixture was cooled to rt, water was added, and extracted with ethyl acetate (×3). The combined organic extracts were washed successively with water, NaHCO<sub>3</sub> soln (aq.), brine, and dried over anhydrous MgSO<sub>4</sub>. The solvent was evaporated in vacuo, and the crude residue purified by flash column chromatography.

**General Procedure F: Preparation of *O*-pentafluorobenzoyl Amidoximes**

To a solution of the amidoxime (1 equiv) and TEA (1.2 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at 0 °C, was added C<sub>6</sub>F<sub>5</sub>COCl (1.2 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and the mixture was stirred for 2 h at the same temperature. Water was added and the mixture extracted with CH<sub>2</sub>Cl<sub>2</sub> (×3). The combined organic extracts were washed with water, NaHCO<sub>3</sub> soln (aq.), brine, dried over anhydrous MgSO<sub>4</sub>, evaporated in vacuo, and the crude residue purified by flash column chromatography.

**General Procedure G: Amino-Heck<sup>9</sup> Preparation of Imidazoles**

Pd(PPh<sub>3</sub>)<sub>4</sub> (0.01 equiv) was added to a solution of the *O*-pentafluorobenzoyl amidoxime (1 equiv) and TEA (5 equiv) in dry DMF (0.05 M) under argon atmosphere at rt. The reaction mixture was warmed to 80 °C and stirring was continued for 30 min to 1 h (the progress of the reaction being monitored by TLC). The reaction mixture was cooled to rt, quenched by adding water and extracted with Et<sub>2</sub>O (×3). The combined extracts were washed with water,

brine ( $\times 2$ ), dried over anhydrous  $\text{MgSO}_4$ , evaporated in vacuo, and the residue purified by flash column chromatography.

#### General Procedure H: Preparation of aryl alkynyl Ketones

The ketone *N,N*-dimethyl hydrazone (1.5 equiv) was treated with freshly prepared LDA (1.5 equiv) [from *n*-BuLi and *N,N*-diisopropylamine in THF (25 mL)] at 0 °C and stirred for 1 h under argon atmosphere. The reaction mixture was then cooled to -78 °C and a solution of 4-bromo-1-butyne **5.31** (1 equiv) in THF was added slowly. The reaction was stirred continuously, warmed to rt overnight and quenched by adding aqueous sat.  $\text{NH}_4\text{Cl}$  solution. The reaction mixture was then extracted with diethyl ether ( $\times 3$ ). The combined organic fractions were washed with water, brine, dried over anhydrous  $\text{MgSO}_4$  and evaporated in vacuo to give crude alkylated hydrazone which was used in the next step without further purification.

To a mixture of acetic acid (5 equiv), sodium acetate (1 equiv), water (2 equiv), and THF (2 equiv) was added the crude alkylated hydrazone,<sup>6</sup> and the mixture was stirred at rt for three hours. The reaction was quenched by adding aqueous NaOH solution at 0 °C and the mixture was extracted with ether ( $\times 3$ ). The combined organic extracts were washed with water, brine, dried over anhydrous  $\text{MgSO}_4$  and evaporated in vacuo. The crude product was purified by flash column chromatography to give the pure alkynyl ketone.

#### General Procedure I: Preparation of Pyrroles by Amino-Heck Reaction

$\text{Pd}(\text{PPh}_3)_4$  (0.01 equiv) was added to a mixture of **5.38** (or **5.39**, 1 equiv), TEA (5 equiv) in dry DMF (0.05 M) under argon atmosphere at rt. The reaction mixture was warmed to 80-90 °C and stirred for the time specified in the experimental section. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to rt, diluted by adding water and extracted with  $\text{Et}_2\text{O}$  ( $\times 3$ ). The combined extracts were washed with water, then



brine (×2), dried over anhydrous  $\text{MgSO}_4$ , and evaporated in vacuo. The residue was purified by preparative thin layer chromatography to give the desired pyrrole.

**General Procedure J: Preparation of Pyrroles by Amino-Heck Reaction Followed by Transmetallation<sup>10</sup>**

The organometallic reagent (1.2-2 equiv) was added slowly to the reaction mixture containing **5.38** (or **5.39**, 1 equiv), TEA (5 equiv) in dry solvent (DMF or THF, 0.05 M) under argon atmosphere at rt, over a period of time specified in the experimental section. The mixture was stirred at rt or at 80-90 °C for the time specified in the experimental section. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to rt, filtered through a celite pad, quenched by adding water and extracted with  $\text{Et}_2\text{O}$  (×3). The combined extracts were washed with water, then brine (×2), dried over anhydrous  $\text{MgSO}_4$ , and evaporated in vacuo. The residue was purified by flash column chromatography to give the desired pyrrole.

**General Procedure K: Preparation of Pyrroles by Amino-Heck Reaction Followed by Intermolecular Heck reaction**

$\text{Pd}(0)$  catalyst (0.01 equiv) was added to a mixture of **5.38** (or **5.39**, 1 equiv), TEA (5 equiv) and methyl acrylate (2 equiv) in dry DMF (0.05 M) under argon atmosphere at rt. The reaction mixture was stirred at 80-90 °C for the time specified in the experimental section. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to rt, diluted by adding water and extracted with  $\text{Et}_2\text{O}$  (×3). The combined extracts were washed with water, then brine (×2), dried over anhydrous  $\text{MgSO}_4$ , and evaporated in vacuo. The residue was purified by flash column chromatography to give the desired pyrrole.

**General Procedure L: Preparation of Pyrroles by Amino-Heck Reaction Followed by Carbonylation-Termination via Alcohol Sequence<sup>10</sup>**

Pd(PPh<sub>3</sub>)<sub>4</sub> (0.01 equiv) was added to a mixture of **5.38** (or **5.39**, 1 equiv), TEA (5 equiv) and alcohol (5 equiv) in dry DMF (0.05 M) under argon atmosphere at rt. CO was then bubbled through the solution for 10 min. The reaction mixture was stirred at 25-70 °C for the time specified in the experimental section under a balloon of CO. The progress of reaction was monitored by TLC. The reaction mixture was cooled to rt, quenched by adding water and extracted with Et<sub>2</sub>O (×3). The combined extracts were washed with water, then brine (×2), dried over anhydrous MgSO<sub>4</sub>, and evaporated in vacuo. The residue was purified by flash column chromatography to give the desired pyrrole.

**General Procedure M: Couplings Using 1,3-(Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride/1-hydroxybenzotriazole Hydrate<sup>11</sup>**

EDCI (1 equiv), HOBT (2 equiv) and base (3.0 equiv) were added to a solution of the acid (1.0 equiv) and amine (1.0 equiv) in dry solvent (~0.1 M, DMF or DCM) under an argon atmosphere with stirring at rt. After stirring for 16 h, the solution was diluted with water and EA (10 mL). The organic phase was separated and the aqueous phase was extracted with EA (×3) and combined organic fractions were washed successively with H<sub>2</sub>O, NaHCO<sub>3</sub> soln (aq.), brine, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to give the crude diene. This was purified by column chromatography.

**Modified General Procedure M**

The reaction was performed in the manner described in General Procedure M, except that DCC was used instead of EDCI. See individual experiments for details.

**General Procedure N: Couplings using benzotriazole-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate<sup>12</sup> (BOP)**

BOP (1 equiv) and DIPEA (3 equiv) were added to a solution of the acid (1 equiv) and amine (1 equiv) in DCM (20 mL) under argon according to the general procedure. The mixture was stirred at rt for the specified time (see experimental for details). Additional equivalents of BOP were added in portions to the reaction mixture to increase the rate of reaction in the forward direction. The solution was diluted with water and EA (10 mL), organic layer separated and aqueous layer back extracted with EA (×3). The combined organic fractions were washed successively with H<sub>2</sub>O, NaHCO<sub>3</sub> soln (aq.), brine and dried (MgSO<sub>4</sub>). Evaporation in vacuo gave the crude diene which were purified by column chromatography.

**General Procedure O: Ring-Closing Metathesis**

The catalyst (either **6.2**, **6.3**, or **6.4**, 0.08 equiv), dissolved in dry degassed DCM, was added to a solution of diene (1.0 equiv) dissolved in dry degassed DCM under argon. The solution was refluxed for the specified time (see experimental for details). Water was added to dilute the reaction mixture, organic layer separated and aqueous layer back extracted with DCM (×3), washed with brine and evaporated in vacuo to give the crude cyclic product. Purification by flash column chromatography gave the desired olefinic product.

**General Procedure P: Preparation of Epoxide<sup>13</sup> Analogues**

To a solution of the olefinic lactam (1 equiv) in acetone (12 mL) and water (10 mL) was added sodium hydrogen carbonate (34 equiv). The mixture was stirred vigorously for 15 min at rt and then cooled to 0 °C, and Oxone® (10 equiv) was added portion-wise over 5 min. The resulting mixture was vigorously stirred at this temperature for 2 h and then at room temperature for 16 h. The acetone was removed under reduced pressure before ethyl

acetate (50 mL) and water were added (50 mL). The organic layer was separated, and the aqueous layer was back-extracted with ethyl acetate ( $\times 3$ ). The combined organic fractions were dried ( $\text{MgSO}_4$ ), filtered, and concentrated, and the resulting residue was purified by silica gel column chromatography.

**General Procedure Q: Preparation of *cis*-diol analogues using Sharpless<sup>14</sup> AD.**

Potassium osmate (0.05 equiv) was added to a heterogeneous slurry of the olefinic lactam (1 equiv), *t*-butyl alcohol (3 mL), water (3 mL), potassium carbonate (3 equiv), potassium ferricyanide (3 equiv), ligand **7.21** or **7.22** (0.05 equiv) and methane sulphonamide (2 equiv) under argon at 0° C. The mixture was stirred for 48 h and warmed to rt. The mixture was cooled to 0° C, sodium sulphite was added and allowed to warm to rt and stirred for 1-2 h. EA was added to the reaction mixture: organic layer was separated and the aq. phase further extracted with EA. The combined organic layers were washed with 2 N KOH, dried ( $\text{MgSO}_4$ ) and concentrated to give the diol and the ligand, which were purified by flash column chromatography.

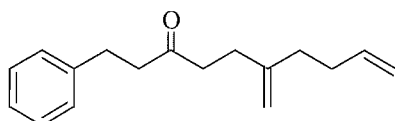
**Modified General Procedure Q: Preparation of *cis*-diol analogues using Sharpless conditions in the absence of ligands.**

The reaction was performed in the manner described in General Procedure Q, except that the reaction was carried out in the absence of ligands **7.21** or **7.22**. See individual experiments for details.

### 8.3 Experimental Work Described in Chapter Three

Dienyl bromide **3.14a**<sup>5</sup> and trienyl chloride **3.14b**<sup>5</sup> were prepared by literature methods.

#### 6-methylene-1-phenyl-9-decen-3-one (**3.15a**)



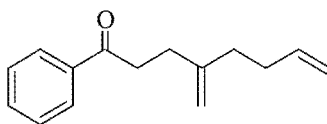
4-Phenyl-2-butanone *N,N*-dimethyl hydrazone (1.75 g, 9.2 mmol) was treated with freshly prepared LDA [from *n*-BuLi (1.6 M in hexane, 3.9 mL) and *N,N*-diisopropylamine (9.2 mL) in THF (25 mL)] at 0 °C and stirred for 1 h under argon atmosphere. **3.14a** (1.07 g, 6.2 mmol) in THF (4 mL) was added according to general procedure A. The crude alkylated hydrazone was then hydrolyzed by adding acetic acid (3.4 mL, 69 mmol), sodium acetate (1.89 g, 13.9 mmol), water (500  $\mu$ L), and THF (2.2 mL) and the mixture was stirred at rt for 3 h. The crude product was purified by flash column chromatography [H/EA = 95/5 then 90/10] to give 540 mg (55%) of **3.15a** as a yellow oil.

FTIR (KBr) 1716, 1643, 1604, 1496, 1454, 1365, 1282, 1187, 1091, 910, 748, 700  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz)  $\delta$  2.08 (t,  $J$  = 7.5 Hz, 2H), 2.16-2.20 (m, 2H), 2.27 (t,  $J$  = 7.5 Hz, 2H), 2.53 (t,  $J$  = 7.5 Hz, 2H), 2.74 (t,  $J$  = 7.6 Hz, 2H), 2.90 (t,  $J$  = 7.7 Hz, 2H), 4.67 (s, 1H), 4.74 (s, 1H), 4.95 (dd,  $J$  = 10.2 Hz, 1.5 Hz, 1H), 4.95 (dd,  $J$  = 10.2 Hz, 1.6 Hz, 1H), 5.01 (dd,  $J$  = 17.1 Hz, 1.5 Hz, 1H), 5.75-5.83 (m, 1H), 7.16-7.20 (m, 3H), 7.25-7.28 (t,  $J$  = 7.4 Hz, 2H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  29.7, 29.8, 31.9, 35.6, 41.2, 44.3, 109.4, 114.6, 126.1, 128.3, 128.5, 138.2, 141.1, 147.7, 209.3.

Micro. Found: C, 83.96; H, 8.98%. Calcd. for  $\text{C}_{17}\text{H}_{22}\text{O}$ : C, 84.25; H, 9.15%.

**4-Methylene-1-phenyl-7-octen-1-one (3.15b)**

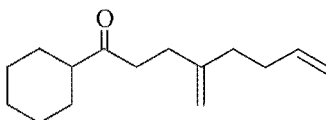
Acetophenone *N,N*-dimethyl hydrazone (1.17 g, 7.20 mmol) was treated with freshly prepared LDA [from *n*-BuLi (1.6 M in hexane, 3 mL) and *N,N*-diisopropyl amine (1.0 mL) in THF (25 mL)] at 0 °C and stirred for 1 h under argon atmosphere. Compound **3.14a** (840 mg) in THF (4 mL) was added according to general procedure A. The crude alkylated hydrazone was then hydrolyzed by adding acetic acid (3.1 mL, 54 mmol), sodium acetate (1.47 g, 10.8 mmol), water (400  $\mu$ L), and THF (1.8 mL) and the mixture was stirred at rt for 5 h. After work up **3.15b** was purified by flash column chromatography (H/EA = 95/5) to give 600 mg (62%) of **3.15b** as a yellow oil.

FTIR (KBr) 1689, 1643, 1596, 1581, 1448, 1355, 1278, 1205, 1180, 989, 906, 744, 690, 507  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz)  $\delta$  2.14-2.17 (m, 2H), 2.20-2.24 (m, 2H), 2.45 (t,  $J = 7.7$  Hz, 2H), 3.12 (t,  $J = 7.7$  Hz, 2H), 4.77 (s, 1H), 4.79 (s, 1H), 4.96 (d,  $J = 10.5$  Hz, 1H), 5.02 (dd,  $J = 17.0$  Hz, 1.6 Hz, 1H), 5.81 (ddt,  $J = 17.0$  Hz, 10.5 Hz, 6.5 Hz, 1H), 7.45 (dd,  $J = 7.2$  Hz, 8.5 Hz, 2H), 7.55 (t,  $J = 7.2$  Hz, 1H), 7.96 (dd,  $J = 8.5$  Hz, 1.5 Hz, 2H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  30.1, 32.0, 35.7, 36.9, 109.4, 114.7, 128.0, 128.6, 133.0, 136.9, 138.2, 147.9, 199.7

Micro. Found: C, 83.84; H, 8.52%, Calcd. for  $\text{C}_{15}\text{H}_{18}\text{O}$ : C, 84.06; H, 8.46%.

**2-(2-Methylene-5-hexenyl) cyclohexanone (3.15c)**

Cyclohexanone *N,N*-dimethyl hydrazone (1.34 g, 8.57 mmol) was treated with freshly prepared LDA [from *n*-BuLi (1.6 M in hexane, 5.7 mL) and *N,N*-diisopropylamine (1.2 mL, 8.57 mmol) in THF (25 mL)] at 0 °C and stirred for 1 h under argon atmosphere. Compound **3.14a** (1.0 g, 5.71 mmol) in THF (4 mL) was added according to general procedure A. The crude alkylated hydrazone was then hydrolyzed by adding acetic acid (2.5 mL, 42.85 mmol), sodium acetate (1.17 g, 8.57 mmol), water (300  $\mu$ L), and THF (1.4 mL) and the mixture was stirred at rt for 2.5 h. The crude product was purified by flash column chromatography (H/EA = 92/8) to give 800mg (63%) of **3.15c** as a colorless oil.

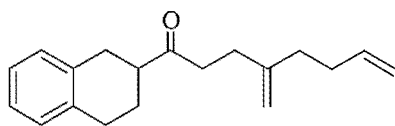
FTIR (KBr), 1712, 1641, 1448, 1338, 1313, 1224, 1128, 998, 908, 811, 636  $\text{cm}^{-1}$

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.26-1.34 (m, 1H), 1.60-1.73 (m, 2H), 1.87 (dd,  $J$  = 14.8 Hz, 8.8 Hz, 2H), 2.02-2.07 (m, 3H), 2.09-2.25 (m, 3 H), 2.29-2.35 (m, 1H), 2.39-2.49 (m, 2H), 2.61 (dd,  $J$  = 14.8 Hz, 4.8 Hz, 1H), 4.70 (s, 1H), 4.79 (s, 1H), 4.95 (d,  $J$  = 7.1 Hz, 1H), 5.02 (dd,  $J$  = 17.1 Hz, 1.6 Hz, 1H), 5.77-5.82 (m, 1H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  24.8, 28.0, 31.9, 33.4, 35.2, 35.7, 42.0, 48.5, 110.8, 114.6, 138.3, 146.5, 212.8.

Micro. Found: C, 81.17; H, 10.29%. Calcd. for  $\text{C}_{13}\text{H}_{20}\text{O}$ : C, 81.19; H, 10.48%.

### 2-(2-Methylene-5-hexenyl)-3,4-dihydro-2H-naphthalene-1-one (**3.15d**)



Tetralone *N,N*-dimethyl hydrazone<sup>6</sup> (1.02 g, 6.92 mmol) was treated with freshly prepared LDA [from *n*-BuLi (1.6 M in hexane, 5.3 mL) and *N,N*-diisopropylamine (960  $\mu$ L, 6.92 mmol) in THF (25 mL)] at 0 °C and stirred for 1 h under argon atmosphere. Compound **3.14a** (810 mg, 4.61 mmol) in THF (4 mL) was added according to general procedure A. The crude alkylated hydrazone was then hydrolyzed by adding acetic acid (2.0 mL, 34.6 mmol), sodium acetate (941 mg, 6.92 mmol), water (400  $\mu$ L), and THF (1.6 mL) and the

mixture was stirred at rt for 2.5 h. The crude product was purified by flash column chromatography (H/EA = 90/10) to give 650 mg (50%) of **3.15d** as a colorless oil.

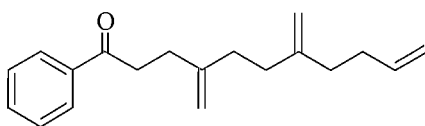
FTIR (KBr), 1683, 1641, 1600, 1484, 1454, 1432, 1355, 1295, 1218, 1157, 1029, 998, 902, 773, 742, 669, 628  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.74-1.82 (m, 1H), 2.09 (dd,  $J$  = 14.5 Hz, 9.8 Hz, 1H), 2.13 (t,  $J$  = 7.5 Hz, 2H), 2.18-2.29 (m, 3H), 2.63 (ddd,  $J$  = 15.1 Hz, 10.2 Hz, 4.3 Hz, 1H), 2.87 (dd,  $J$  = 14.5, 3.9 Hz, 1H), 2.92-3.02 (m, 2H), 4.80 (s, 1H), 4.87 (s, 1H), 4.97 (dd,  $J$  = 10.2 Hz, 1.2 Hz, 1H), 5.04 (dd,  $J$  = 17.1 Hz, 1.6 Hz, 1H), 5.79-5.87 (m, 1H), 7.23 (d,  $J$  = 7.6 Hz, 1H), 7.29 (t,  $J$  = 7.5 Hz, 1H), 7.45 (dt,  $J$  = 7.5 Hz, 1.2 Hz, 1H), 8.03 (d,  $J$  = 7.7 Hz, 1H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  27.7, 28.3, 31.8, 34.8, 36.1, 45.4, 111.6, 114.6, 126.5, 127.4, 128.7, 132.4, 133.1, 138.2, 144.0, 146.4, 199.8.

Micro. Found: C, 84.75; H, 8.33%, Calcd. for  $\text{C}_{17}\text{H}_{20}\text{O}$ : C, 84.95; H, 8.32%.

#### 4,7-Dimethylene-1-phenyl-10-undecen-1-one (**3.15g**)



Acetophenone *N,N*-dimethyl hydrazone<sup>6</sup> (696 mg, 4.29 mmol) was treated with freshly prepared LDA [from *n*-BuLi (1.6 M in hexane, 1.8 mL) and *N,N*-diisopropylamine (600  $\mu\text{L}$ , 4.29 mmol) in THF (25 mL)] at 0  $^{\circ}\text{C}$  and stirred for 1 h under argon atmosphere. The trienyl chloride **3.14b** (530 mg, 2.86 mmol) in THF (4 mL) was added according to general procedure A. The crude alkylated hydrazone was then hydrolyzed by adding acetic acid (2.5 mL, 42.89 mmol), sodium acetate (1.17 g, 8.57 mmol), water (300  $\mu\text{L}$ ), and THF (1.4 mL) and the mixture was stirred at rt for 5 h. The crude product was purified by flash column chromatography (H/EA = 98/2) to give 620 mg (81%) of **3.15g** as a colorless oil.

FTIR (KBr), 1687, 1643, 1596, 1581, 1448, 1357, 1321, 1203, 1180, 1000, 985, 908, 889, 744, 690, 502  $\text{cm}^{-1}$ .

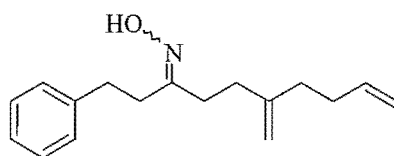


$^1\text{H}$  NMR (500 MHz)  $\delta$  1.99 (t,  $J = 7.5$  Hz, 1H), 2.11-2.24 (m, 2H), 2.16-2.20 (m, 6H), 2.47 (t,  $J = 7.5$  Hz, 2H), 3.13 (t,  $J = 7.8$  Hz, 2H), 4.75 (s, 1H), 4.76 (s, 1H), 4.77 (s, 1H), 4.80 (s, 1H), 4.96 (d,  $J = 10.5$  Hz, 1H), 5.03 (dd,  $J = 17.2$  Hz, 1.5 Hz, 1H), 5.78-5.86 (m, 1H), 7.46 (t,  $J = 7.7$  Hz, 2H), 7.56 (t,  $J = 7.4$  Hz, 1H), 7.79 (d,  $J = 7.4$  Hz, 2H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  30.1, 32.0, 34.4, 34.7, 35.4, 36.9, 109.2, 109.3, 114.5, 128.0, 128.6, 133.0, 136.9, 138.4, 148.3, 148.7, 199.7.

Micro. Found: C, 85.05; H, 8.93%, Calcd. for  $\text{C}_{19}\text{H}_{24}\text{O}$ : C, 85.02; H, 9.01%.

**(*EZ*)-6-Methylene-1-phenyl-9-decene-3-one oxime (3.16a)**



The dienyl ketone **3.15a** (1.37 g, 5.7 mmol), hydroxylamine hydrochloride (530 mg, 7.6 mmol) and pyridine (700  $\mu\text{L}$ , 8.5 mmol) were stirred in EtOH (30 mL) at rt for 1 h according to the general procedure B. The crude oxime (1:1 mixture, based on analysis of  $^1\text{H}$  NMR spectrum) was purified by flash column chromatography (H/EA = 90/10) to give 1.41 g (97%) of (*EZ*)-**3.16a** (1:1) as an inseparable mixture of oximes as a pale yellow oil.

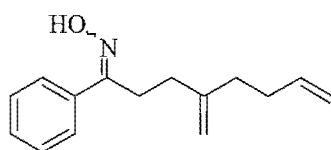
Data for (*E/Z*) - **3.16a**

FTIR (KBr) 1643, 1604, 1496, 1454, 1299, 1166, 1078, 1031, 997, 962, 910, 748, 700, 555  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz)  $\delta$  2.01 (t,  $J = 7.4$  Hz, 1H), 2.07-2.19 (m, 6H), 2.42-2.46 (m, 2H), 2.57 (dd,  $J = 8.5$  Hz, 5.5 Hz, 1H), 2.78 (dd,  $J = 16.5$  Hz, 10.0 Hz, 2H), 4.66 (s, 0.5 H), 4.68 (s, 0.5 H), 4.70 (s, 0.5 H), 4.71 (s, 0.5 H), 4.88 (dd,  $J = 10.1$  Hz, 1.6 Hz, 1H), 4.96 (dd,  $J = 17.1$  Hz, 1.8 Hz, 1H), 5.69-5.78 (m, 1H), 7.07-7.20 (m, 3H), 7.21 (t,  $J = 7.6$  Hz, 2H), 8.46 (bs, 1H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  26.5, 30.0, 31.5, 31.6, 31.9, 31.9, 32.3, 32.5, 33.0, 35.3, 35.4, 36.0, 109.7, 109.7, 114.6, 126.1, 126.1, 128.3, 128.4, 138.3, 141.3, 141.4, 147.9, 148.1, 160.7.  
Micro. Found: C, 79.04; H, 9.10; N, 5.34%. Calcd. for  $\text{C}_{17}\text{H}_{23}\text{NO}$ : C, 79.33; H, 9.00; N, 5.44%.

**(*E/Z*)<sup>15</sup> - 4-Methylene-1-phenyl-7-octen-1-one oxime (3.16b)**



The dienyl ketone **3.16b** (222 mg, 1.03 mmol), hydroxylamine hydrochloride (153 mg, 2.15 mmol) and pyridine (220  $\mu\text{L}$ , 2.58 mmol) were stirred in EtOH (30 mL) at rt for 2 h according to general procedure B. The crude (*EZ*)-**3.16b** (8:1.5, based on analysis of  $^1\text{H}$  NMR spectrum) was purified by column chromatography (H/EA = 90/10) to elute 166 mg (70%) of *E*-**3.16b** as a yellow oil first, and then 32.5 mg (14%) of *Z*-**3.16b** as a yellow oil, thus yielding the oxime in a combined yield of 84%.

**Data for *E*-3.16b**

FTIR (KBr) 1643, 1597, 1578, 1448, 1345, 1155, 1075, 989, 906, 744, 690  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz)  $\delta$  2.14-2.20 (m, 4H), 2.27 (t,  $J = 8.1$  Hz, 2H), 2.94 (t,  $J = 8.2$  Hz, 2H), 4.78 (s, 1H), 4.81 (s, 1H), 4.95 (d,  $J = 10.2$  Hz, 1H), 5.01 (dd,  $J = 17.5$  Hz, 1.3 Hz, 1H), 5.76-5.84 (m, 1H), 7.37-7.39 (m, 3H), 7.58-7.60 (m, 2H), 8.49 (bs, 1H).

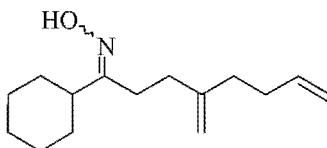
$^{13}\text{C}$  NMR (125 MHz)  $\delta$  24.9, 31.9, 32.3, 35.3, 109.7, 114.6, 126.3, 128.7, 129.2, 135.6, 138.4, 148.2, 159.5.

Micro. Found: C, 78.28; H, 8.41; N, 6.17, Calcd. for  $\text{C}_{15}\text{H}_{19}\text{NO}$ : C, 78.56; H, 8.35; N, 6.11%.

Data for **Z-3.16b**

$^1\text{H}$  NMR (500 MHz)  $\delta$  2.01-2.21 (m, 6H), 2.68 (t,  $J = 8.0$  Hz, 2H), 4.73 (s, 1H), 4.76 (s, 1H), 4.92-5.00 (m, 2H), 5.73-5.81 (m, 1H), 7.37-7.39 (m, 3H), 7.34-7.43 (m, 5H), 8.69 (bs, 1H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  24.7, 31.9, 32.4, 35.4, 109.7, 114.6, 126.3, 128.7, 129.2, 135.6, 138.4, 148.2, 159.5.

**(*EZ*)-2-(2-Methylene-5-hexenyl) cyclohexanone oxime (3.16c)**

The dienyl ketone **3.15c** (280 mg, 1.47 mmol), hydroxylamine hydrochloride (154 mg, 2.21 mmol) and pyridine (230  $\mu\text{L}$ , 2.94 mmol) were stirred in EtOH (30 mL) at rt for 1 h according to general procedure B. The crude (*EZ*)-**3.16c** (4:2, based on analysis of  $^1\text{H}$  NMR spectrum) was purified by flash column chromatography (H/EA = 90/10) to give 181 mg (60%) of *E*-**3.16c** as a colorless oil, as well as 91 mg (30%) of *Z*-**3.16c** as a yellow oil.

Data for *E*-**3.16c**

FTIR (KBr) 1641, 1444, 1351, 1249, 1145, 997, 939, 908, 823, 767, 665  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.36-1.40 (m, 1H), 1.42-1.52 (m, 1H), 1.54-1.62 (m, 1H), 1.65-1.76 (m, 2H), 1.84 (ddd,  $J = 4.3$  Hz, 8.1 Hz, 12.2 Hz, 1H), 2.05-2.09 (m, 3H), 2.15-2.22 (m, 2H), 2.26 (ddd,  $J = 4.5$  Hz, 9.0 Hz, 14.0 Hz, 1H), 2.41 (ddd,  $J = 13.5$  Hz, 8.5 Hz, 4.8 Hz, 1H), 2.47 (dd,  $J = 13.8$  Hz, 5.4 Hz, 1H), 2.75-2.81 (m, 1H), 4.74 (s, 1H), 4.80 (s, 1H), 4.95 (dd,  $J = 10.2$  Hz, 1.6 Hz, 1H), 5.02 (dd,  $J = 17.2$  Hz, 1.7 Hz, 1H), 5.77-5.85 (m, 1H), 8.73 (bs, 1H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  23.3, 23.6, 26.1, 31.8, 32.0, 34.8, 37.5, 39.6, 111.3, 114.5, 138.4, 146.5, 162.7.

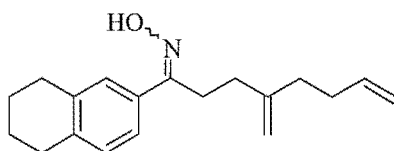
Micro. Found: C, 75.14; H, 10.15; N, 6.72%, Calcd. for  $C_{13}H_{21}NO$ : C, 75.31; H, 10.20; N, 6.75%.

Data for **Z-3.16c**

$^1H$  NMR (500 MHz)  $\delta$  1.37-1.50 (m, 2H), 1.52-1.61 (m, 2H), 1.72-1.75 (m, 1H), 1.86-1.90 (m, 1H), 2.14-2.31 (m, 8H), 3.63-3.67 (m, 1H), 4.79 (s, 2H), 4.93-5.05 (m, 2H), 5.78-5.86 (m, 1H), 9.07 (bs, 1H).

$^{13}C$  NMR (125 MHz)  $\delta$  20.4, 26.8, 28.1, 28.7, 30.1, 31.8, 34.4, 36.7, 111.5, 114.4, 138.5, 146.4, 163.0.

**(E)-2-(2-Methylene-5-hexenyl)-3, 4-dihydronaphthalene-1(2H)-one oxime (3.16d)**



The dienyl ketone **3.15d** (165 mg, 0.69 mmol), hydroxylamine hydrochloride (120 mg, 1.73 mmol) and pyridine (140  $\mu$ L, 1.73 mmol) were stirred in EtOH (30 mL) at rt for 1 h according to general procedure B. The crude oxime **3.16d** (single isomer, based on analysis of  $^1H$  NMR spectrum) was purified by flash column chromatography (H/EA = 90/10) to give 141 mg (80%) of **(E)-3.16d** as a white solid.

FTIR (KBr) 1644, 1598, 1488, 1454, 1353, 1313, 1124, 1095, 1054, 1037, 964, 892, 767, 730, 665  $cm^{-1}$ .

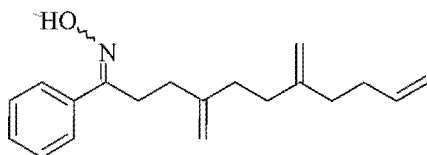
$^1H$  NMR (500 MHz)  $\delta$  1.78-1.92 (m, 2H), 2.13 (q,  $J$  = 13.7 Hz, 11.1 Hz, 1H), 2.20 (t,  $J$  = 5.8 Hz, 1H), 2.23-2.26 (m, 2H), 2.32 (m, 1H), 2.50 (dd,  $J$  = 4.2 Hz, 13.8 Hz, 1H), 2.65 (td,  $J$  = 16.7 Hz, 4.0 Hz, 1H), 2.95 (ddd,  $J$  = 17.1 Hz, 11.9 Hz, 5.3 Hz, 1H), 3.74-3.79 (m, 1H), 4.80 (s, 1H), 4.85 (s, 1H), 4.97 (d,  $J$  = 10.3 Hz, 1H), 5.05 (dd,  $J$  = 17.3 Hz, 1.1 Hz, 1H),

5.81-5.89 (m, 1H), 7.15 (d,  $J = 7.5$  Hz, 1H), 7.19 (t,  $J = 7.4$  Hz, 1H), 7.27 (dt,  $J = 7.6$  Hz, 1.0 Hz, 1H), 7.88 (d,  $J = 7.5$  Hz, 1H), 9.23 (bs, 1H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  23.9, 24.7, 29.5, 31.9, 34.4, 35.0, 111.9, 114.5, 124.4, 126.3, 128.9, 129.2, 129.9, 138.5, 138.7, 146.5, 158.2.

Micro. Found: C, 79.68; H, 8.29; N, 5.42%. Calcd for  $\text{C}_{17}\text{H}_{20}\text{NO}$ : C, 79.96; H, 8.28, N, 5.48%.

**(*EZ*)-4,7-Dimethylene-1-phenyl-10-undecen-1-one oxime (3.16g)**



The trienyl ketone **3.15g** (540 mg, 2.01 mmol), hydroxylamine hydrochloride (329 mg, 4.7 mmol) and pyridine (400  $\mu\text{L}$ , 5.03 mmol) were stirred in EtOH (30 mL) at rt for 3 h according to general procedure B. The crude (*EZ*)-**3.16g** (9:1, based on analysis of  $^1\text{H}$  NMR spectrum) mixture was purified by flash column chromatography (H/EA = 93/7) to give 480 mg (84%) of (*E*)-**3.16g** as a colorless oil as well as 63 mg (11%) of (*Z*)-**3.16g** as a yellow oil.

Data for (*E*)-**3.16g**

FTIR (KBr) 1949, 1643, 1598, 1575, 1498, 1446, 1319, 1303, 1157, 1070, 998, 931, 890, 765, 694  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz)  $\delta$  2.10 (t,  $J = 7.5$  Hz, 2H), 2.14-2.21 (m, 6H), 2.28 (t,  $J = 8.2$  Hz, 2H), 2.96 (t,  $J = 8.1$  Hz, 2H), 4.73 (s, 2H), 4.79 (s, 1H), 4.80 (s, 1H), 4.95 (dd,  $J = 10.3$  Hz, 1.2 Hz, 1H), 5.02 (dd,  $J = 17.2$  Hz, 1.7 Hz, 1H), 5.77-5.85 (m, 1H), 7.37-7.40 (m, 3H), 7.58-7.60 (m, 2H) 9.20 (bs, 1H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  24.9, 31.9, 32.2, 34.3, 34.3, 35.4, 109.3, 109.5, 114.5, 126.3, 128.6, 129.2, 135.5, 138.4, 148.5, 148.7, 159.4.

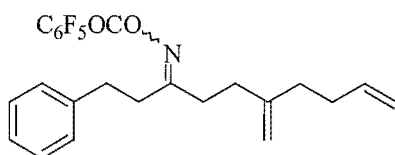
Micro. Found: C, 80.24; H, 8.75; N, 4.85%. Calcd for  $C_{19}H_{25}NO$ : C, 80.52; H, 8.75; N, 4.94%.

Data for (Z)-3.16g

$^1H$  NMR (500 MHz)  $\delta$  2.06-2.11 (m, 4H), 2.16-2.22 (m, 4H), 2.64-2.72 (m, 2H), 4.71-4.76 (m, 4H), 4.95 (dd,  $J = 10$  Hz, 1 Hz, 1H), 5.00-5.02 (m, 1H), 5.76-5.85 (m, 1H), 7.36-7.43 (m, 5H), 8.68 (bs, 1H).

$^{13}C$  NMR (125 MHz)  $\delta$  31.9, 32.7, 33.8, 34.2, 34.2, 35.4, 109.2, 109.5, 109.7, 114.5, 127.7, 128.2, 128.5, 128.9, 133.2, 138.4, 147.9, 148.6, 158.3.

(*EZ*)-6-Methylene-1-phenyl-9-decene-3-one *O*-pentafluorobenzoyloxime (3.17a)



To a solution of (*EZ*)-3.16a [(1:1), 1.41 g, 5.5 mmol] and TEA (1.6 mL, 10.9 mmol) in DCM (20 mL) at 0 °C was added  $C_6F_5COCl$  (1.6 g, 7.1 mmol) in DCM (5 mL) and stirred for 30 min according to general procedure C. The crude (*EZ*)-3.17a (1:1, based on  $^1H$  NMR) was purified by flash column chromatography (H/EA = 95:5) to give 2.29 g (95%) of an inseparable mixture of (*EZ*)-3.17a (1:1, based on analysis of  $^1H$  NMR spectrum) as a pale yellow oil.

Data for (*EZ*)-3.17a

FTIR (KBr) 1760, 1650, 1523, 1506, 1454, 1417, 1326, 1189, 1091, 1002, 906, 862, 750, 700, 509  $cm^{-1}$ .

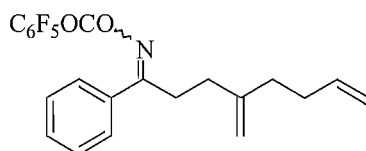
$^1H$  NMR (500 MHz)  $\delta$  2.01 (t, 7.4 Hz, 1H), 2.07-2.19 (m, 6H), 2.42-2.46 (m, 2H), 2.57 (dd,  $J = 8.5$  Hz, 5.5 Hz, 1H), 2.78 (dd,  $J = 16.5$  Hz, 10.0 Hz, 2H), 4.66 (s, 0.5 H), 4.68 (s, 0.5 H),

4.70 (s, 0.5 H), 4.71 (s, 0.5 H), 4.88 (dd,  $J = 10.1$  Hz, 1.6 Hz, 1H), 4.96 (dd,  $J = 17.1$  Hz, 1.8 Hz, 1H), 5.69-5.78 (m, 1H), 7.07-7.20 (m, 3H), 7.21 (t,  $J = 7.6$  Hz, 2H), 8.46 (bs, 1H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  26.4, 29.9, 31.5, 31.6, 31.9, 31.9, 32.3, 32.5, 33.0, 35.3, 35.4, 36.0, 109.7, 109.7, 114.6, 126.1, 126.1, 128.3, 128.4, 138.3, 141.3, 141.4, 147.9, 148.1, 160.7.

Micro. Found: C, 64.08; H, 5.04; N, 3.08%. Calcd for  $\text{C}_{24}\text{F}_5\text{H}_{22}\text{NO}_2$ : C, 63.85; H, 4.91; N, 3.10%.

**(*E*)-4-Methylene-1-phenyl-7-octen-1-one *O*-pentafluorobenzoyloxime (3.17b)**



To a solution of *E*-3.16b (146 mg, 0.63 mmol) and TEA (330  $\mu\text{L}$ , 2.4 mmol) in DCM (20 mL) at 0 °C was added  $\text{C}_6\text{F}_5\text{COCl}$  (235 mg, 1.02 mmol) in DCM (5 mL) and stirred for 1.5 h according to general procedure C. The crude oxime was purified by silica chromatography (H/EA = 95/5) to give 233mg (87%) of (*E*)-3.17b as a white solid.

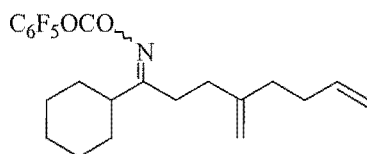
Data for (*E*)-3.17b

FTIR (KBr), 1766, 1648, 1523, 1498, 1444, 1419, 1326, 1195, 1095, 1004, 946, 904, 865, 769, 694  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz)  $\delta$  2.11-2.14 (m, 4H), 2.27 (t,  $J = 8.3$  Hz, 2H), 3.03 (t,  $J = 8.3$  Hz, 2H), 4.78 (s, 1H), 4.80 (s, 1H), 4.91-4.97 (m, 2H), 5.70-5.79 (m, 1H), 7.44 (t,  $J = 7.3$  Hz, 2H), 7.49 (t,  $J = 7.3$  Hz, 1H), 7.74 (d,  $J = 7.5$  Hz, 2H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  27.5, 31.7, 32.7, 35.0, 107.0, 110.4, 114.6, 127.4, 127.6, 128.0, 128.6, 128.8, 131.1, 132.9, 136.7-136.9 (overlapping m), 137.9, 138.7-138.9, 142.4-142.5, 144.4-144.5, 146.4-146.5 (overlapping m), 146.9, 156.5, 168.4.

Micro. Found: C, 62.29; H, 4.42; N, 3.38%, Calcd for  $\text{C}_{22}\text{F}_5\text{H}_{18}\text{NO}_2$ : C, 62.41; H, 4.28; N, 3.31%.

**(*E*)-2-(2-Methylene-5-hexenyl) cyclohexanone *O*-pentafluorobenzoyloxime (3.17c)**

To a solution of the *E*-3.16c (111 mg, 0.57 mmol) and TEA (160  $\mu$ L, 1.14 mmol) in DCM (20 mL) at 0 °C was added  $\text{C}_6\text{F}_5\text{COCl}$  (171 mg, 0.74 mmol) in DCM (5 mL) and stirred for 2 h according to general procedure C. The crude product was purified by flash column chromatography (H/EA = 95:5) to give 176 mg (77%) of *E*-3.17c as a clear oil along with 20% of recovered starting material.

Data for *E*-3.17c

FTIR (KBr), 1752, 1652, 1523, 1508, 1448, 1419, 1326, 1197, 1141, 1093, 1002, 873, 759, 698  $\text{cm}^{-1}$ .

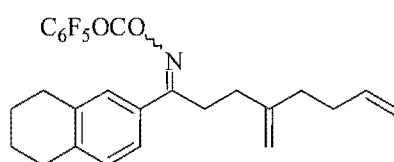
$^1\text{H}$  NMR (500 MHz)  $\delta$  1.54-1.62 (m, 2H), 1.68-1.78 (m, 3H), 1.87-1.93 (m, 1H), 2.11 (t,  $J$  = 7.5 Hz, 2H), 2.15-2.25 (m, 3H), 2.52 (ddd,  $J$  = 13.6 Hz, 6.5 Hz, 6.5 Hz, 2H), 2.62-2.66 (m, 1H), 2.67-2.74 (m, 1H), 4.79 (s, 1H), 4.84 (s, 1H), 4.96 (d,  $J$  = 10.1 Hz, 1H), 5.03 (dd,  $J$  = 17.1 Hz, 1.45 Hz, 1H), 5.77-5.85 (m, 1H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  22.6, 25.9, 26.4, 31.6, 31.8, 34.7, 37.2, 39.9, 107.5 (complex), 11.8, 114.6, 137.7 (d complex,  $J$  = 254 Hz), 138.2, 143.2 (d complex,  $J$  = 258 Hz), 145.3 (d complex,  $J$  = 250 Hz), 145.8, 156.9, 173.1.

Micro. Found: C, 60.06; H, 5.11; N, 3.55%. Calcd for  $\text{C}_{20}\text{F}_5\text{H}_{20}\text{NO}_2$ : C, 59.84; H, 5.02, N, 3.48%.



**(*E*)-2-(2-Methylene-5-hexenyl)-3,4-dihydronaphthalene-1(2*H*)-one *O*-pentafluorobenzoyloxime (3.17d)**



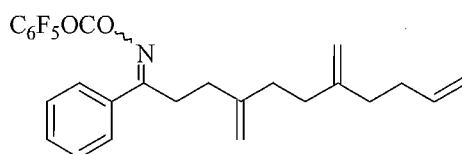
To a solution of the *E*-3.16d (97 mg, 0.38 mmol) and TEA (115  $\mu$ L, 0.76 mmol) in DCM (15 mL) at 0 °C was added  $C_6F_5COCl$  (114 mg, 0.49 mmol) in DCM (5 mL) and stirred for 2 h according to general procedure C. The crude product was purified by flash column chromatography (H/EA = 95:5) to give 142 mg (75%) of (*E*)-3.17d as a white solid.

FTIR (KBr), 1762, 1652, 1523, 1452, 1417, 1326, 1251, 1193, 1091, 1002, 946, 904, 865, 769, 730  $cm^{-1}$ .

$^1H$  NMR (500 MHz)  $\delta$  1.87-1.95 (m, 2H), 2.02-2.13 (m, 4H), 2.20 (dd,  $J$  = 14.0 Hz, 10.5 Hz, 1 H), 2.31 (dd,  $J$  = 13.8 Hz, 5.2 Hz, 1H), 2.71 (dt,  $J$  = 16.7 Hz, 4.0 Hz, 1H), 2.97 (ddd,  $J$  = 17.3 Hz, 11.6 Hz, 6.0 Hz, 1H), 3.65-3.70 (m, 1H), 4.77 (s, 1H), 4.84 (s, 1H), 4.87 (s, 2H), 4.91 (dd,  $J$  = 8.2 Hz, 1.4 Hz, 2H), 5.65-5.73 (m, 1H), 7.17 (d,  $J$  = 7.7 Hz, 1H), 7.23 (t,  $J$  = 7.5 Hz, 1H), 7.36 (dt,  $J$  = 7.5 Hz, 1.2 Hz, 1H), 8.15 (d,  $J$  = 7.7 Hz, 1H).

$^{13}C$  NMR (125 MHz)  $\delta$  24.0, 24.2, 31.7, 31.9, 34.1, 35.7, 107.4, 112.8, 114.5, 126.3, 126.5, 126.6, 127.5, 129.1, 131.4, 137.7 (d complex,  $J$  = 255 Hz), 137.80, 140.0, 143.4 (d complex,  $J$  = 271 Hz), 145.1, 145.2 (d complex,  $J$  = 257 Hz), 156.5, 166.5.

Micro. Found: C, 63.87; H, 4.57; N, 3.16%. Calcd for  $C_{24}F_5H_{20}NO_2$ : C, 64.14; H, 4.48, N, 3.11%.

**(*E*)-4, 7-Dimethylene-1-phenyl-10-undecen-1-one *O*-pentafluorobenzoyloxime (3.17g)**

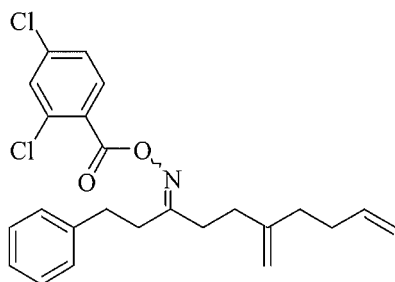
To a solution of the trienyl ketone oxime *E*-3.16g (359 mg, 1.26 mmol) and TEA (350  $\mu$ L, 2.53 mmol) in DCM (20 mL) at 0 °C was added  $\text{C}_6\text{F}_5\text{COCl}$  (496 mg, 2.14 mmol) in DCM (5 mL) and stirred for 2 h at that temperature according to general procedure C. The crude product was purified by flash column chromatography (H/EA = 98:2) to give 486 mg (80%) of (*E*)-3.17g as a clear viscous oil.

FTIR (KBr), 1760, 1650, 1604, 1521, 1506, 1455, 1417, 1324, 1197, 1091, 1002, 948, 865, 750, 698  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz)  $\delta$  2.04-2.10 (m, 4H), 2.12-2.18 (m, 4H), 2.28 (t,  $J$  = 7.9 Hz, 2H), 3.04 (t,  $J$  = 8.2 Hz, 2H), 4.66 (s, 1H), 4.70 (s, 1H), 4.77 (s, 1H), 4.80 (s, 1H), 4.95 (d,  $J$  = 10.9 Hz, 1H), 5.01 (dd,  $J$  = 17.1 Hz, 1.5 Hz, 1H), 5.75-5.83 (m, 1H), 7.44 (t,  $J$  = 7.4 Hz, 2H), 7.49 (t,  $J$  = 7.3 Hz, 1H), 7.74 (d,  $J$  = 7.2 Hz, 2H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  27.5, 31.9, 32.8, 34.0, 34.1, 35.3, 107.0 (complex), 109.1, 110.2, 114.5, 127.4, 128.8, 131.1, 133.0, 137.7 (d complex,  $J$  = 242 Hz), 138.2, 143.4 (d complex,  $J$  = 246 Hz), 145.4 (d complex,  $J$  = 260 Hz), 143.7, 148.4, 156.4, 168.3.

Micro. Found: C, 65.70; H, 5.28; N, 2.94%. Calcd for  $\text{C}_{24}\text{F}_5\text{H}_{24}\text{NO}_2$ : C, 65.40; H, 5.06, N, 2.93%.

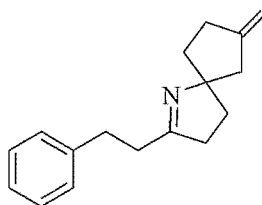
**(*EZ*)-6-Methylene-1-phenyl-9-decene-3-one *O*-2,4-dichlorobenzoyloxime (3.17h)**

To a solution of the dienyl ketone oxime **3.16a** (265 mg, 1.03 mmol) and TEA (300  $\mu$ L, 2.06 mmol) in DCM (15 mL) at 0 °C was added *O*-2,4-dichlorobenzoyl chloride (0.2, 1.34 mmol) in DCM (5 mL) and stirred for 30 min according to general procedure C. The crude product (1:1, based on analysis of  $^1\text{H}$  NMR spectrum) was purified by flash column chromatography (H/EA = 95:5) to give 400 mg (90%) of an inseparable mixture of (*E/Z*)-**3.17h** (1:1) as a cream solid.

Data for (*E/Z*)-**3.17h**

$^1\text{H}$  NMR (500 MHz)  $\delta$  2.10 (t,  $J$  = 7.4 Hz, 2H), 2.11-2.19 (m, 2H), 2.23 (t,  $J$  = 8 Hz, 1H), 2.30 (t,  $J$  = 8 Hz, 1H), 2.43 (t,  $J$  = 6.5 Hz, 1H), 2.59 (t,  $J$  = 7.5 Hz, 1H), 2.70-2.76 (m, 2H), 2.87 (t,  $J$  = 7.5 Hz, 1H), 2.96 (t,  $J$  = 7.5 Hz, 1H), 4.76 (s, 1 H), 4.79 (s, 0.5 H), 4.80 (s, 0.5 H), 4.93-4.98 (m, 1H), 5.00 (m, 0.5 H), 5.02 (m, 0.5H), 5.73-5.84 (m, 1H), 7.17-7.32 (m, 8H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  28.7, 31.7, 31.8, 31.9, 32.0, 32.2, 32.3, 43.9, 35.2, 36.0, 110.2, 110.5, 114.7, 126.4, 126.6, 128.1, 128.3, 128.5, 128.6, 136.1, 137.9, 138.0, 139.4, 139.8, 140.3, 141.7, 143.6, 145.0, 146.7, 147.0, 147.1, 156.5, 170.9, 171.0.

**7-Methylene-2-phenethyl-1-aza-spiro[4.4]non-1-ene (3.18a)**

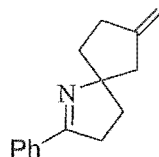
$\text{Pd}(\text{PPh}_3)_4$  (26 mg, 0.020 mmol) was added to a suspension of (*E/Z*)-**3.17a** (102 mg, 0.20 mmol), TEA (200  $\mu\text{L}$ , 1.1 mmol) and molecular sieves 4Å (150 mg) in dry DMF (0.05 M) under argon atmosphere at rt and stirred at 110 °C for 30 min according to general procedure D. The residue was purified by flash column chromatography (H/EA = 95/5-90/10) to give 42 mg (77%) of **3.17a** as a yellow oil.

FTIR (KBr) 1641, 1604, 1496, 1454, 1428, 1311, 1085, 1031, 875, 750, 700  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz),  $\delta$  1.62 (ddd,  $J = 12.5$  Hz, 7.3 Hz, 5.5 Hz, 1H), 1.71-1.79 (m, 2H), 1.93 (dd,  $J = 8.5$  Hz, 12.0 Hz, 1H), 2.22 (d,  $J = 15.5$  Hz, 1H), 2.34-2.40 (m, 1H), 2.46-2.49 (t,  $J = 7.7$  Hz, 2H), 2.56 (dd,  $J = 17.5$  Hz, 2.0 Hz, 2H), 2.63 (t,  $J = 7.8$  Hz, 2H), 2.90 (t,  $J = 7.9$  Hz, 2H), 4.87 (s, 2H), 7.17 (d,  $J = 7.2$  Hz, 1H), 7.21 (d,  $J = 7.2$  Hz, 2H), 7.27 (t,  $J = 7.5$  Hz, 2H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  31.3, 32.9, 34.4, 35.4, 37.3, 39.0, 46.3, 82.1, 106.1, 125.7, 128.3, 128.3, 141.3, 150.9, 175.2.

HRMS [FAB $^+$ ] [MH] $^+$ : Found: 240.1727; Calcd for  $\text{C}_{17}\text{H}_{22}\text{N}$ : 240.1727.

**7-Methylene-2-phenyl-1-aza-spiro[4.4]non-1-ene (3.18b)**

$\text{Pd}(\text{PPh}_3)_4$  (20 mg, 0.017 mmol) was added to a suspension of *E*-**3.17b** (73.4 mg, 0.17 mmol), TEA (120  $\mu\text{L}$ , 0.86 mmol) and molecular sieves 4 $\text{\AA}$  (150 mg) in dry DMF (0.05 M) under argon atmosphere at rt and stirred at 110  $^\circ\text{C}$  for 30 min according to general procedure D. The residue was purified by preparative thin layer chromatography (H/EA = 8/2) to give 29.5 mg (82%) of **3.18b** as a yellow oil.

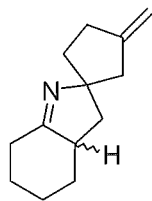
FTIR (KBr), 1660, 1614, 1575, 1494, 1448, 1428, 1340, 1299, 1240, 1340, 1299, 1178, 1074, 1029, 919, 875, 759, 692, 557  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.73 (ddd,  $J = 12.5$  Hz, 7.5 Hz, 4.5 Hz, 1H), 1.91-1.96 (m, 2H), 2.09 (ddd,  $J = 12.2$  Hz, 8.6 Hz, 3.6 Hz, 1H), 2.33 (d,  $J = 15.9$  Hz, 1H), 2.39-2.46 (m, 1H), 2.62-2.67 (m, 1H), 2.71 (dd,  $J = 15.8$  Hz, 1.9 Hz, 1H), 2.99 (t,  $J = 7.5$  Hz, 2H), 4.91 (s, 2H), 7.37-7.40 (m, 3H), 7.82 (dd,  $J = 7.3$  Hz, 1.8 Hz, 2H).

$^{13}\text{C}$  NMR (125 MHz) ( $\text{CDCl}_3$ );  $\delta$  31.4, 34.4, 34.9, 39.2, 46.5, 82.8, 106.1, 127.7, 128.3, 130.2, 134.8, 151.0, 170.6.

Micro. Found: C, 85.02; H, 8.17; N, 6.57, Calcd for  $\text{C}_{15}\text{H}_{17}\text{N}$ : C, 85.26; H, 8.10; N, 6.62%.

**3',3'a,4',5',6',7'-hexahydro-3-methylene-spiro[cyclopentane-1,2'-[2*H*]indole] (3.18c)**



$\text{Pd}(\text{PPh}_3)_4$  (13.5 mg, 0.012 mmol) was added to a suspension of *E*-**3.17c** (47 mg, 0.12 mmol), TEA (80  $\mu\text{L}$ , 0.58 mmol) and molecular sieves 4 $\text{\AA}$  (150 mg) in dry DMF (0.05 M) under argon atmosphere at rt and stirred at 110  $^\circ\text{C}$  for 30 min according to general procedure D. The residue was purified by flash column chromatography (H/Acetone = 85/15) to give 14 mg (64%) of diastereomer mixture (1:1, based on analysis of  $^1\text{H}$  NMR spectrum) of **3.18c** as a yellow oil.

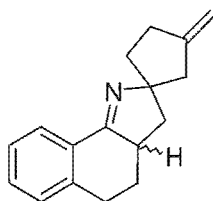
FTIR (KBr), 1654, 1648, 1430, 1348 1309, 1276, 1166, 1083, 1029, 977, 873, 804  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.08-1.18 (m, 1H), 1.32-1.49 (m, 3H), 1.58-1.64 (m, 0.5 H), 1.67-1.86 (m, 2H), 1.93-2.02 (m, 1H), 2.03-2.27 (m, 4H), 2.27-2.42 (m, 2H), 2.49-2.78 (m, 3.5 H), 4.83-4.94 (m, 2H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  25.28, 25.30, 26.7, 26.8, 31.26, 31.30, 31.9, 34.9, 35.0, 38.8, 40.6, 41.7, 41.9, 46.2, 47.9, 48.0, 48.2, 80.5, 80.6, 106.0, 106.1, 151.0, 177.1.

HRMS FAB  $[\text{MH}]^+$ : Found: 190.1562; Calcd for  $\text{C}_{13}\text{H}_{20}\text{N}$ : 190.1596

**3,3a,4,5-tetrahydro-3'-methylene-spiro[2H-benz[g]indole-2,1'-cyclopentane] (3.18d)**



$\text{Pd}(\text{PPh}_3)_4$  (20.8 mg, 0.018 mmol) was added to a suspension of *E*-**3.17d** (82 mg, 0.18 mmol), TEA (130  $\mu\text{L}$ , 0.91 mmol) and molecular sieves 4 $\text{\AA}$  (150 mg) in dry DMF (0.05 M) under argon atmosphere at rt and stirred at 110  $^\circ\text{C}$  for 30 min according to general procedure D. The residue was purified by preparative thin layer chromatography (H/EA = 80/20) to give 34.5 mg (80%) of diastereomer mixture (1:1, based on analysis of  $^1\text{H}$  NMR spectrum) of **3.18d** as a yellow oil.

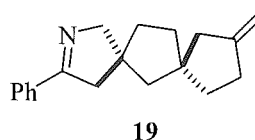
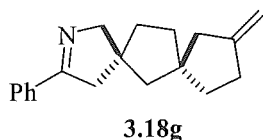
FTIR (KBr), 1658 1619, 1602, 1569, 1481, 1459, 1430, 1355, 1342, 1274, 1247, 1153, 1074, 1029, 871, 767, 730, 663  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.48 (dd,  $J = 19.8$  Hz, 8.8 Hz, 1H), 1.63 (dd,  $J = 12.9$  Hz, 4.6 Hz, 1H), 1.55-1.75 (m, 1.5 H), 1.77-1.83 (m, 1H), 2.19-2.45 (m, 5H), 2.56-2.70 (m, 1H), 2.85-3.06 (m, 3.5 H), 4.80-4.93 (m, 2H), 7.17 (d,  $J = 7.6$  Hz, 1H), 7.22 (t,  $J = 7.5$  Hz, 1H), 7.31 (t,  $J = 7.4$  Hz, 1H), 8.10 (d,  $J = 7.7$  Hz, 1H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  29.9, 29.9, 29.9, 30.0, 31.4, 31.4, 37.1, 40.4, 42.2, 42.3, 44.5, 46.6, 46.7, 47.7, 80.9, 80.9, 105.9, 106.1, 126.1, 126.3, 128.7, 130.2, 130.3, 130.5, 140.8, 151.0, 151.1, 171.5.

Micro. Found: C, 85.74; H, 8.11; N, 6.09%. Calcd for  $\text{C}_{17}\text{H}_{19}\text{N}$ : C, 86.02; H, 8.06, N, 5.90%.

### 9-Methylene-2-phenyl-1-aza-dispiro[4.1.4.2]tridec-1-ene (**3.18g** and **19**)



$\text{Pd}(\text{PPh}_3)_4$  (23.6 mg, 0.02 mmol) was added to a suspension of *E*-**3.17g** (98 mg, 0.20 mmol), TEA (140  $\mu\text{L}$ , 1.0 mmol) and molecular sieves 4Å (150 mg) in dry DMF (0.05 M) under argon atmosphere at rt and stirred at 110 °C for 30 min according to the general procedure D. The residue was purified by preparative thin layer chromatography (H/Et<sub>2</sub>O = 80/20) to give 24 mg (44%) of the major isomer (**18g** or **19**) as a yellow oil, and 18 mg (33%) of the minor isomer (**18g** or **19**) as a low *R<sub>f</sub>* fraction. Thus, **3.18g** and **19** were isolated in a combined yield of 77%, and the configuration was not assigned.

Data for major isomer

FTIR (KBr), 1658, 1614, 1575, 1494, 1448, 1428, 1342, 1305, 1176, 1014, 987, 917, 875, 759, 692, 665, 559.

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.63-1.70 (m, 2H), 1.71-1.87 (m, 4H), 1.96-2.08 (m, 4H), 2.29 (s, 2H), 2.35 (t,  $J$  = 8.2 Hz, 2H), 2.92-2.96 (m, 2H), 4.83-4.86 (m, 2H), 7.36-7.40 (m, 3H), 7.81-7.83 (m, 2H).

$^{13}\text{C}$  NMR (125 MHz)  $\delta$  31.4, 34.9, 36.9, 37.7, 39.7, 40.1, 47.7, 50.0, 51.4, 83.3, 105.4, 127.6, 128.3, 130.1, 135.0, 152.8, 169.5.

Micro. Found: C, 85.74; H, 8.69; N, 5.14%. Calcd for C<sub>19</sub>H<sub>23</sub>N: C, 85.98; H, 8.73, N, 5.27%.

Data for minor isomer

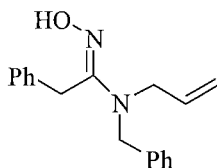
<sup>1</sup>H NMR (500 MHz)  $\delta$  1.60-1.81 (m, 6H), 1.84 (ddd,  $J$  = 12.8 Hz, 5.5 Hz, 7.6 Hz, 1H), 1.95-2.07 (m, 4H), 2.34-2.41 (m, 3H), 2.89-2.98 (m, 2H), 4.82 (s, 1H), 4.86(s, 1H), 7.36-7.41 (m, 3H), 7.82 (dd,  $J$  = 7.7 Hz, 1.8 Hz, 2H).

<sup>13</sup>C NMR (125 MHz) (CDCl<sub>3</sub>)  $\delta$  = 31.5, 34.9, 36.9, 37.8, 39.6, 40.0, 47.8, 50.0, 51.4, 109.3, 114.5, 127.6, 128.0, 128.6, 133.0, 152.5, 169.0 .

## 8.4 Experimental Work Described in Chapter Four

Oximes **4.9a**,<sup>16</sup> **4.9bb**,<sup>17</sup> **4.18a-c**<sup>18</sup> and hydroxamoyl chloride **4.10c**<sup>19</sup> were prepared by the literature methods.

### (*E*)-1-*N*-allyl-*N*-benzyl-*N'*-hydroxy-2-phenylethanimidamide (**4.11a**)



(*E/Z*)-**4.9a** (1:1) (400 mg, 2.96 mmol), NCS (400 mg, 2.99 mmol) and *N*-allyl benzyl amine (849 mg, 3.55 mmol) in dry DMF (25 mL) were reacted according to general method E and the residue purified by flash column chromatography (PE/EA = 9/1 then 8/2) to give 525 mg (63%) of (*E*)-**4.11a** as a yellow crystalline solid.

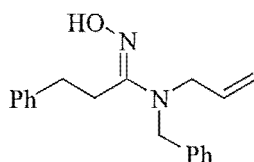
<sup>1</sup>H NMR (500 MHz)  $\delta$  3.72 (d,  $J$  = 5.5Hz, 2H, NCH<sub>2</sub>CH), 3.98 (s, 2H, PhCH<sub>2</sub>CN), 4.32 (s, 2H, NCH<sub>2</sub>Ph), 5.09 (dd,  $J$  = 22 Hz, 10 Hz, 2H, CHCH<sub>2</sub>), 5.67-5.75 (m, 1H, CHCH<sub>2</sub>), 7.13 (d,  $J$  = 8 Hz, 2H, Ar), 7.20-7.23(m, 2H, Ar), 7.26-7.34 (m, 6H, Ar).



$^{13}\text{C}$  NMR (75 MHz)  $\delta$  30.4 ( $\text{PhCH}_2\text{CN}$ ), 49.9 ( $\text{NCH}_2\text{CH}$ ), 50.4 ( $\text{NCH}_2\text{Ph}$ ), 116.8 ( $\text{CHCH}_2$ ), 126.4, 126.9, 127.1, 128.3, 128.5, 128.6 (Ar), 133.5 ( $\text{CHCH}_2$ ), 136.2, 138.3 (Ar), 159.1 ( $\text{C}=\text{N}$ ).

TOF MS  $\text{ES}^+[\text{MH}]^+$ : Found. 281.2135; Calcd for  $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}$ : 281.1654.

**(*E*)-1-*N*-allyl-*N*-benzyl-*N*'-hydroxy-3-phenyl propanimidamide (4.11b)**



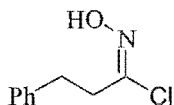
(a) (*E/Z*)-**4.10b** (3:2) (235 mg, 1.57 mmol), NCS (211 mg, 1.59 mmol) and *N*-allyl benzyl amine (276 mg, 1.88 mmol) in dry DMF (25 mL) were reacted according to general method E and the residue purified by flash column chromatography (PE/EA = 9/1 then 8/2) to give 370 mg (61%) of (*E*)-**4.11b** as a cream solid.

$^1\text{H}$  NMR (500 MHz)  $\delta$  2.80-2.94 (m, 2H,  $\text{CH}_2\text{CH}_2$ ), 3.73 (d,  $J$  = 5.5 Hz, 2H,  $\text{NCH}_2\text{CH}$ ), 4.31 (s, 2H,  $\text{NCH}_2\text{Ph}$ ), 5.08-5.16 (m, 2H,  $\text{CHCH}_2\text{N}$ ), 5.74-5.82 (m, 1H,  $\text{CHCH}_2$ ), 7.20 (t,  $J$  = 7.5 Hz, 4H, Ar), 7.23-7.33 (m, 6H, Ar).

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  27.0 ( $\text{PhCH}_2$ ), 32.6 ( $\text{PhCH}_2\text{CH}_2$ ), 49.9 ( $\text{NCH}_2\text{CH}$ ), 50.5 ( $\text{PhCH}_2\text{N}$ ), 116.8 ( $\text{CH}_2\text{CH}$ ), 126.2, 127.0, 127.2, 128.4, 128.4, 128.5 (Ar), 133.8 ( $\text{CH}_2\text{CH}$ ), 138.4, 141.4 (Ar), 160.8 ( $\text{C}=\text{N}$ ).

TOF MS  $\text{ES}^+[\text{MH}]^+$ : Found: 295.1694; Calcd for  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}$ : 295.1810.

**(b) (*E*)-3-phenylpropanoyl chloride oxime (4.10b)**



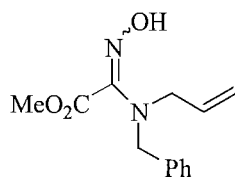
(*E/Z*)-**4.9b** (3:2) (1.87 g, 12.61 mmol), and NCS (1.68 mg, 12.61 mmol) in dry DMF (25 mL) were reacted according to the modified general method E. Work up as for **4.11b** gave 2.0 g (87%) of (*E*)-**3b** as a yellow oily solid.

<sup>1</sup>H NMR mixture (300 MHz)  $\delta$  2.77–2.82 (m, 2H, PhCH<sub>2</sub>CH<sub>2</sub>), 2.94–2.99 (m, 2H, PhCH<sub>2</sub>CH<sub>2</sub>), 7.18–7.32 (m, 5H, Ar), 8.15 (bs, 1H, OH).

A solution of (*E*)-**4.10b** (50 mg, 0.27 mmol) and *N*-allyl benzyl amine (40 mg, 0.27 mmol) in dry DMF (20 mL) was stirred at 50–70° C for 2 h. Workup as described in general procedure E, followed by purification by flash column chromatography (PE/EA = 9/1 then 8/2) gave 56 mg (66%) of (*E*)-**4.11b** as a cream solid.

<sup>1</sup>H NMR & <sup>13</sup>C NMR data as above.

**(*EZ*)-Methyl 2-[allyl(benzyl)amino](hydroxyimino)acetate (**4.11c**)**



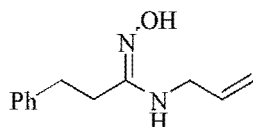
A solution of (*E/Z*)-**4.10c** (6:5) (502 mg, 4.0 mmol) and *N*-allyl benzyl amine (586 mg, 4.0 mmol) in dry DMF (20 mL) was stirred at 50–70° C for 2 h. Workup as described in general procedure E, followed by purification by flash column chromatography (PE/EA = 80/40) gave 748 mg (75%) of (*EZ*)-**4.11c** (6:5, based on analysis of <sup>1</sup>H NMR spectrum) as a yellow solid.

<sup>1</sup>H NMR (300 MHz):  $\delta$  3.63 (d, *J* = 6 Hz, 2H, NCH<sub>2</sub>CH, major), 3.73 (s, 3H, CH<sub>3</sub>, minor), 3.78 (d, *J* = 7 Hz, 2H, CH<sub>2</sub>CHCH<sub>2</sub>, minor), 3.89 (s, 3H, CH<sub>3</sub>, major), 4.26 (s, 2H, NCH<sub>2</sub>Ph, major), 4.44 (s, 2H, NCH<sub>2</sub>Ph, minor), 5.09–5.21 (m, 2H, CHCH<sub>2</sub>, minor & major), 5.69–5.93 (m, 1H, CHCH<sub>2</sub>, minor & major), 7.23–7.35 (m, 5H, Ar, minor & major), 7.49 (bs, 1H, C=NOH, major), 9.16 (bs, 1H, C=NOH, minor).

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  49.7 ( $\text{NCH}_2\text{CH}$ , minor), 50.8 ( $\text{NCH}_2\text{Ph}$ , minor), 52.4 ( $\text{CH}_3$ , minor), 52.7 ( $\text{CH}_3$ , major), 52.6 ( $\text{NCH}_2\text{CH}$ , major), 53.5 ( $\text{NCH}_2\text{Ph}$ , major), 117.9 ( $\text{CHCH}_2$ , major), 118.3 ( $\text{CHCH}_2$ , minor), 127.2, 127.5, 127.8, 128.0, 128.4, 128.5, ( $\text{Ar}$ , major & minor), 132.1, 134.4 ( $\text{NCH}_2\text{CHCH}_2$ , major & minor), 136.3 ( $\text{Ar}$ , minor), 137.9 ( $\text{Ar}$ , minor & major), 146.4 ( $\text{C}=\text{O}$ , major), 154.4 ( $\text{C}=\text{O}$ , minor), 162.5 ( $\text{C}=\text{N}$ , major), 162.7 ( $\text{C}=\text{N}$ , minor).

TOF MS  $\text{ES}^+ [\text{MH}]^+$ : Found: 249.1142; Calcd for  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}$ : 249.1239.

**(1-*EZ*)-*N*-allyl-*N'*-hydroxy-3-phenylpropanimidamide (4.14)**

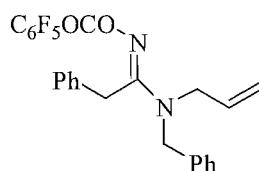


(*E/Z*)-**4.9b** (3:2) (399 mg, 2.67 mmol), NCS (357 mg, 2.67 mmol) and allyl amine (276 mg, 1.88 mmol) in dry DMF (25 mL) were reacted according to general method E and the residue purified by flash column chromatography (PE/EA = 10/20) to give 441 mg (81%) of (*E*)-**4.14** as a colorless oil.

$^1\text{H}$  NMR mixture (300 MHz)  $\delta$  2.38 (t,  $J$  = 13.5 Hz, 2H,  $\text{PhCH}_2$ ), 2.79 (t,  $J$  = 13.5 Hz, 2H,  $\text{CH}_2\text{CH}_2$ ), 3.62 (m, 2H,  $\text{NHCH}_2$ ), 4.99-5.16 (m, 2H,  $\text{CHCH}_2$ ), 5.35 (bs, 1H,  $\text{NH}$ ), 5.54-5.56 (m, 1H,  $\text{CHCH}_2$ ), 7.08-7.20 (m, 5H,  $\text{Ar}$ ), 8.76 (bs, 1H,  $\text{C}=\text{NOH}$ ).

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  30.3 ( $\text{PhCH}$ ), 32.8 ( $\text{PhCHCH}$ ), 44.2 ( $\text{NHCH}_2$ ), 115.5 ( $\text{CHCH}_2$ ), 125.9, 128.1, 128.3 ( $\text{Ar}$ ), 135.5 ( $\text{CHCH}_2$ ), 141.0 ( $\text{Ar}$ ), 154.6 ( $\text{C}=\text{N}$ ).

TOF MS  $\text{ES}^+ [\text{EI}]^+$ : Found: 204.1262; Calcd for  $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}$ : 204.12626.

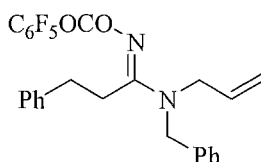
**(*E*)-1-*N*-allyl-*N*-benzyl-2-phenyl-*N*'-[(pentafluorobenzoyl)oxy] ethanimid amide (4.12a)**

A solution of (*E*)-4.11a (461 mg, 1.64 mmol), TEA (300  $\mu$ L, 2.14 mmol), and  $\text{C}_6\text{F}_5\text{COCl}$  (492 mg, 2.14 mmol) in dry DCM (30 mL) was reacted as described in general procedure F, and the crude product purified by flash column chromatography (PE/EA = 98/2) to give 650 mg (83%) of (*E*)-4.12a as a colorless oil.

$^1\text{H}$  NMR (500 MHz)  $\delta$  3.87 (d,  $J$  = 5 Hz, 2H,  $\text{NCH}_2\text{CH}$ ), 3.98 (s, 2H,  $\text{PhCH}_2\text{CN}$ ), 4.50 (s, 2H,  $\text{NCH}_2\text{Ph}$ ), 5.16 (dd,  $J$  = 24 Hz, 10 Hz, 2H,  $\text{CHCH}_2$ ), 5.73-5.81 (m, 1H,  $\text{CHCH}_2$ ), 7.19 (t,  $J$  = 8 Hz, 4H, Ar), 7.27 (t,  $J$  = 7 Hz, 2H, Ar), 7.32 (t,  $J$  = 7 Hz, 4H, Ar).

$^{13}\text{C}$  NMR (75 MHz):  $\delta$  = 32.2 ( $\text{PhCH}_2\text{CN}$ ), 50.0 ( $\text{NCH}_2\text{CH}$ ), 50.5 ( $\text{NCH}_2\text{Ph}$ ), 107.9 (m, C-F), 117.6 ( $\text{CHCH}_2$ ), 126.9, 127.3, 127.4, 127.7, 128.6, 129.1, 132.5 (Ar), 134.5 ( $\text{CHCH}_2$ ), 135.7-139.5 (m, C-F), 140.9-144.9 (m, C-F), 143.2-147.1 (m, C-F), 156.9 ( $\text{OCOC}_6\text{F}_5$ ), 164.9 ( $\text{C}=\text{N}$ ).

Micro. Found: C = 63.44, H = 4.08, N = 5.68; Calcd for  $\text{C}_{24}\text{H}_{17}\text{F}_5\text{N}_2\text{O}_2$ : C = 63.29, H = 4.04, N = 5.90.

**(*E*)-1-*N*-allyl-*N*-benzyl-3-phenyl-*N*'-[(pentafluorobenzoyl)oxy] propanimid amide (4.12b)**

A solution of (*E*)-**4.11b** (273 mg, 0.93 mmol), TEA (150  $\mu$ L, 0.99 mmol) and  $\text{C}_6\text{F}_5\text{COCl}$  (229 mg, 0.99 mmol) in dry DCM (30 mL) was reacted as described in general procedure F, and the crude product purified by flash column chromatography (PE/EA = 98/2) to give 393 mg (87%) of (*E*)-**4.12b** as a white solid.

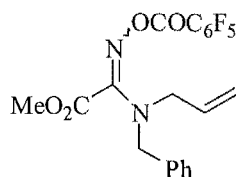
$^1\text{H}$  NMR (500 MHz)  $\delta$  2.81-2.91 (m, 4H,  $\text{CH}_2\text{CH}_2$ ), 3.83 (d,  $J$  = 5.5 Hz, 2H,  $\text{NCH}_2\text{CH}$ ), 4.44 (s, 2H,  $\text{NCH}_2\text{Ph}$ ), 5.12-5.19 (m, 2H,  $\text{CHCH}_2$ ), 5.76-5.83 (m, 1H,  $\text{CHCH}_2$ ), 7.11 (d,  $J$  = 7.5 Hz, 2H, Ar), 7.18-7.29 (m, 6H, Ar), 7.34 (t, 2H,  $J$  = 7 Hz, Ar).

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  28.4 ( $\text{PhCH}_2$ ), 32.8 ( $\text{PhCH}_2\text{CH}_2$ ), 50.1 ( $\text{NCH}_2\text{CH}$ ), 50.5 ( $\text{PhCH}_2\text{N}$ ), 107 (m, C-F), 117.5 ( $\text{CH}_2\text{CH}$ ), 126.5, 127.3, 128.1, 128.5, 128.6 (Ar), 132.6 ( $\text{NCH}_2\text{CH}$ ), 135.7-139.5 (m, C-F), 140.9-144.9 (m, C-F), 143.2-147.1 (m, C-F), 137.1 (Ar), 139.8 (Ar), 156.8 ( $\text{OCOC}_6\text{F}_5$ ), 166.7 ( $\text{C}=\text{N}$ ).

Micro. Found: C = 64.07, H = 4.49, N = 5.70; Calcd: C = 63.87, H = 4.33, N = 5.73.

TOF MS  $\text{ES}^+$   $[\text{MH}]^+$ : Found: 489.1610; Calcd for  $\text{C}_{25}\text{H}_{19}\text{F}_5\text{N}_2\text{O}_2$ : 489.1601.

**(*EZ*)-Methyl-2-[allyl(benzyl)amino]{[(pentafluorobenzoyl) oxy] imino}acetate (**4.12c**)**



A solution of **4.11c** (594 mg, 2.39 mmol), TEA (420  $\mu$ L, 2.75 mmol) and  $\text{C}_6\text{F}_5\text{COCl}$  (634 mg, 2.75 mmol) in dry DCM (30 mL) was reacted as described in general procedure F, and the crude product purified by flash column chromatography (PE/EA = 80/20) to give 835 mg (88%) of (*EZ*)-**4.12c** (4:1 based on analysis of  $^1\text{H}$  NMR spectrum) as a yellow solid.

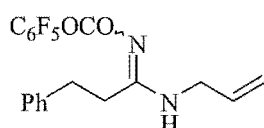
$^1\text{H}$  NMR (500 MHz)  $\delta$  3.85-3.99 (m, 5H,  $\text{NCH}_2\text{CH}$ ,  $\text{CH}_3$ , minor & major), 4.42 (s, 2H,  $\text{NCH}_2\text{Ph}$ , minor), 4.53 (s, 2H,  $\text{NCH}_2\text{Ph}$ , major), 5.16-5.28 (m, 2H,  $\text{CHCH}_2$ , minor & major), 5.75-5.88 (m, 1H,  $\text{CHCH}_2$ , minor & major), 7.18-7.44 (m, 5H, Ar, minor & major).

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  49.7, 50.8, 52.9, 53.6, 54.0, 54.3, 106.8 (m), 119.2, 119.3, 126.7,

127.4, 127.9, 128.1, 128.5, 128.7, 131.1, 132.4, 135.5-147.3 (m), 135.1, 136.2, 135.5-147.3 (m), 151.5, 159.4, 155.4, 156.1, 159.4, 160.1, 161.4 (C=N).

TOF MS ES<sup>+</sup> [M+2]<sup>+</sup>: Found: 443.1023; Calcd for C<sub>20</sub>H<sub>14</sub>F<sub>5</sub>N<sub>2</sub>O<sub>4</sub>: 443.1030.

**(*EZ*)-1-*N*-allyl-3-phenyl-*N'*[(pentafluorobenzoyl)oxy] propanimidamide (4.15)**



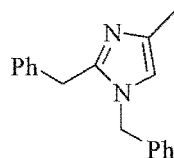
A solution of **4.14** (76 mg, 0.41 mmol), TEA (75  $\mu$ L, 0.53 mmol) and C<sub>6</sub>F<sub>5</sub>COCl (124 mg, 0.53 mmol) in dry DCM (10 mL) was reacted as described in general procedure F, and the crude product purified by flash column chromatography (PE/EA = 80/20) to give 110 mg (90%) of (*E/Z*)-**4.15** (4:1 based on analysis of <sup>1</sup>H NMR spectrum) as a yellow solid.

Data for (*E/Z*)-**4.15**

<sup>1</sup>H NMR (500 MHz)  $\delta$  2.63 (t, *J* = 8.5 Hz, 2H, PhCH<sub>2</sub>, major), 2.69 (t, *J* = 8.5 Hz, 2H, PhCH<sub>2</sub>, minor), 2.93 (t, *J* = 8 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>, minor), 2.98 (t, *J* = 8.5 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>, major), 3.76-3.78 (m, 2H, NHCH<sub>2</sub>, minor), 3.80-3.82 (m, 2H, NHCH<sub>2</sub>, major), 5.09-5.13 (m, 2H, CHCH<sub>2</sub>, minor), 5.22-5.29 (m, 2H, CHCH<sub>2</sub>, major), 5.75-5.80 (m, 1H, CHCH<sub>2</sub>, minor), 5.82-5.89 (m, 1H, CHCH<sub>2</sub>, major), 7.16-7.32 (m, 5H, Ar, major and minor).

<sup>13</sup>C NMR (75 MHz)  $\delta$  30.1 (PhCH<sub>2</sub>, major), 32.5 (PhCH<sub>2</sub>, minor), 32.5 (CH<sub>2</sub>CH<sub>2</sub>, minor), 32.8 (CHCH<sub>2</sub>, major), 44.3 (NHCH, minor), 44.7 (NHCH, major), 116.7 (CHCH<sub>2</sub>, major), 117.2 (CHCH<sub>2</sub>, minor), 126.5 (major, Ar), 126.6 (minor Ar), 128.2, 128.5 (major Ar), 128.6 (minor, Ar), 133.3 (CHCH<sub>2</sub>, minor), 134.0 (CHCH<sub>2</sub>, major), 135.7-147.1 (m, C-F), 139.7 (Ar, minor), 140.2 (Ar, major), 156.2, 160.1 (C=N, major), 164.2 (C=N, minor).

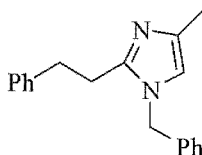
HRP EI<sup>+</sup>[M-1]<sup>+</sup>: Found: 397.0975; Calcd for C<sub>19</sub>H<sub>14</sub>F<sub>5</sub>N<sub>2</sub>O<sub>2</sub>: 397.0975.

**1,2-dibenzyl-4-methyl-1*H*-imidazole (4.13a)**

A mixture of (*E*)-**4.12a** (169 mg, 0.36 mmol), TEA (300  $\mu$ L, 1.78 mmol), and  $\text{Pd}(\text{PPh}_3)_4$  (41 mg, 0.035 mmol) in dry DMF (7 mL) was treated as described in general procedure G with heating at 80  $^\circ\text{C}$  for 30 min. The residue was purified by flash column chromatography {(PE/EA = 60/40 - 10/90 (gradually increasing the gradient))} to give 62 mg (65%) of **4.13a** as a yellow oil.

$^1\text{H}$  NMR (500 MHz)  $\delta$  2.22 (s, 3H,  $\text{CH}_3$ ), 4.02 (s, 2H,  $\text{PhCH}_2$ ), 4.80 (s, 2H,  $\text{NCH}_2\text{Ph}$ ), 6.52 (s, 1H,  $\text{CH}_3\text{CCHN}$ ), 6.92 (dd,  $J = 6$  Hz, 1Hz, 2H, Ar), 7.14 (d,  $J = 7.5$  Hz, 2H, Ar), 7.19 (t,  $J = 7.5$  Hz, 1H, Ar), 7.27 (m, 5H, Ar).

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  13.6 ( $\text{CH}_3$ ), 33.7 ( $\text{PhCH}_2\text{C}=\text{N}$ ), 49.3 ( $\text{NCH}_2\text{Ph}$ ), 116.7 ( $\text{CH}_3\text{CCHN}$ ), 126.5, 126.7, 127.7, 128.2, 128.6, 128.7, 136.3, 136.4 (Ar), 137.3 ( $\text{CH}_3\text{CCHN}$ ), 145.8 ( $\text{C}=\text{N}$ ). TOF MS  $\text{ES}^+ [\text{MH}]^+$ : Found: 263.1436; Calcd for  $\text{C}_{18}\text{H}_{19}\text{N}_2$ : 263.1548.

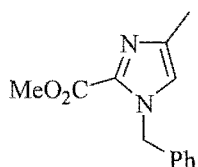
**1-Benzyl-4-methyl-2-(2-phenylethyl)-1*H*-imidazole (4.13b)**

A mixture of (*E*)-**4.12b** (151 mg, 0.31 mmol), TEA (230  $\mu$ L, 1.55 mmol), and  $\text{Pd}(\text{PPh}_3)_4$  (36 mg, 0.031 mmol) in dry DMF (6 mL) was treated as described in general procedure G with heating at 80  $^\circ\text{C}$  for 30 min. The residue was purified by flash column chromatography (PE/EA = 60/40-10/90) to give 53 mg (62%) of **4.13b** as a yellow oil.

$^1\text{H}$  NMR (500 MHz)  $\delta$  2.23 (s, 3H,  $\text{CH}_3$ ), 2.85-3.01 (m, 4H,  $\text{CH}_2\text{CH}_2$ ), 2.99 (t,  $J = 7.5$  Hz, 2H,  $\text{PhCH}_2\text{CH}_2\text{C}=\text{N}$ ), 4.80 (s, 2H,  $\text{NCH}_2\text{Ph}$ ), 6.50 (s, 1H,  $\text{CH}_3\text{CCHN}$ ), 7.00 (d,  $J = 7$  Hz, 2H, Ar), 7.11 (d,  $J = 7.5$  Hz, 2H, Ar), 7.19 (t,  $J = 7.5$  Hz, 1H, Ar), 7.26-7.33 (m, 5H, Ar);  $^{13}\text{C}$  NMR (75 MHz)  $\delta$  13.5 ( $\text{CH}_3$ ), 29.1 ( $\text{PhCH}_2$ ), 34.7 ( $\text{PhCH}_2\text{CH}_2$ ), 49.1 ( $\text{NCH}_2\text{Ph}$ ), 116.1 ( $\text{CH}_3\text{CCHN}$ ), 126.2, 126.7, 127.9, 128.4, 128.5, 128.9, 136.3, 137.3 (Ar), 141.2, ( $\text{CH}_3\text{CCHN}$ ), 147.0 ( $\text{C}=\text{N}$ ).

TOF MS  $\text{ES}^+[\text{MH}]^+$ : Found: 277.1605; Calcd for  $\text{C}_{19}\text{H}_{21}\text{N}_2$ : 277.1705.

#### Methyl 1-benzyl-4-methyl-1*H*-imidazole-2-carboxylate (4.13c)



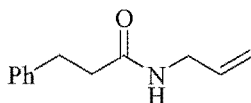
A mixture of (*E/Z*)-4.12c (4:1, 226 mg, 0.51 mmol), TEA (400  $\mu\text{L}$ , 2.55 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (59mg, 0.051 mmol) in dry DMF (9 mL) was treated as described in general procedure G with heating at 80  $^\circ\text{C}$  for 3 h. The residue was purified by flash column chromatography (PE/EA = 60/40) to give (34 mg, 30%) of 6c as a yellow oil.

$^1\text{H}$  NMR (500 MHz)  $\delta$  2.18 (s, 3H,  $\text{CH}_3$ ), 3.84 (s, 3H,  $\text{OCH}_3$ ), 5.51 (s, 2H,  $\text{NCH}_2\text{Ph}$ ), 6.74 (s, 1H,  $\text{CH}_3\text{CCHN}$ ), 7.11 (d,  $J = 7$  Hz, 2H, Ar), 7.19-7.28 (m, 3H, Ar).

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  13.7 ( $\text{CH}_3$ ), 51.3 ( $\text{OCH}_3$ ), 52.2 ( $\text{NCH}_2\text{Ph}$ ), 122.5 ( $\text{CH}_3\text{CCHN}$ ), 127.4, 128.0, 128.8, 134.8 (Ar), 136.4, ( $\text{CH}_3\text{CCHN}$ ), 139.1 ( $\text{CH}_3\text{OCOC}=\text{N}$ ), 159.4 ( $\text{C}=\text{N}$ );

TOF MS  $\text{ES}^+[\text{MH}]^+$ : Found: 231.1181; Calcd for  $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2$ : 231.1134.

#### *N*-allyl-3-phenylpropanamide (4.16)<sup>20</sup>



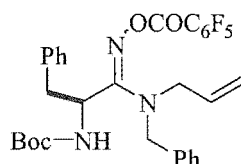


A mixture of (*E/Z*)-**4.15** (104 mg, 0.26 mmol), TEA (180  $\mu$ L, 1.3 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (30 mg, 0.026 mmol) in dry DMF (6 mL) was treated as described in general procedure G with heating at 80 °C for 3 h. The residue was purified by flash column chromatography (PE/EA = 80/20-60/40) to give (46 mg, 94%) of **4.16** as a yellow oil.

<sup>1</sup>H NMR (500 MHz)  $\delta$  2.82 (t, *J* = 7.5 Hz, 2H, PhCH<sub>2</sub>), 3.05 (t, *J* = 8.0 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>), 4.06-4.07 (m, 2H, NHCH<sub>2</sub>), 5.16-5.29 (m, 2H, CHCH<sub>2</sub>), 5.74-5.81 (m, 1H, CHCH<sub>2</sub>), 7.20 (d, *J* = 7.5 Hz, 2H, Ar), 7.26 (d, *J* = 7.5 Hz, 1H, Ar), 7.33 (d, *J* = 7.5 Hz, 2H, Ar).

<sup>13</sup>C NMR (75 MHz)  $\delta$  26.7, 30.9, 44.0, 118.9, 126.9, 128.3, 128.8, 130.2, 139.1, 158.7.

**(*E*)-(*S*)- *tert*-Butyl (1-allyl(benzyl)amino)-1-[(pentafluorobenzoyl)oxy]imino}propan-2-yl-carbamate (**4.21a**)**



A mixture of (*E/Z*)-**4.18a** (2:1, 400 mg, 1.52 mmol), NCS (204 mg, 1.53 mmol) and *N*-allyl benzyl amine (268 mg, 1.82 mmol) in dry DMF (10 mL) were reacted according to general method E and the crude residue (isomer ratio 3:1 determined by analysis of <sup>1</sup>H NMR spectrum) was then subjected to flash column chromatography (PE/EA = 9:1-17:3) to give 300 mg of (*E/Z*)-**4.20a** as a yellow foam, which was not purified further (isomer ratio 5:2 by <sup>1</sup>H NMR).

Selected data for **4.20a**.

TOF MS ES<sup>+</sup>[MH]<sup>+</sup>: Found: 410.2122; Calcd for C<sub>24</sub>H<sub>32</sub>N<sub>3</sub>O<sub>3</sub>: 410.2444.

A sample of (*E/Z*)-**4.20a** (285 mg), TEA (90  $\mu$ L, 0.60 mmol) and C<sub>6</sub>F<sub>5</sub>COCl (138 mg, 0.60 mmol) in dry DCM (15 mL) was reacted as described in general procedure F, and the crude

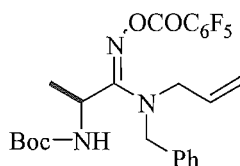
product purified by flash column chromatography (PE/EA = 97/3) to give 210 mg (61%) of (*E*)-**4.21a** as a colorless oil.

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.41 (s, 9H, *t*-Bu), 3.07-3.15 (m, 2H, PhCH<sub>2</sub>CH), 3.70 (dd,  $J$  = 16.5 Hz, 5 Hz, 1H, NCH<sub>2</sub>CH), 3.95 (dd,  $J$  = 16.5 Hz, 5 Hz, 1H, NCH<sub>2</sub>CH), 4.35 (d,  $J$  = 16 Hz, 1H, NCH<sub>A</sub>Ph), 4.45 (d,  $J$  = 16 Hz, 1H, NCH<sub>B</sub>Ph), 4.93 (dd,  $J$  = 17 Hz, 8 Hz, 1H, CH), 5.10 (m, 2H, CHCH<sub>2</sub>), 5.49 (bd,  $J$  = 10 Hz, 1H, NH), 5.60-5.67 (m, 1H, NCH<sub>2</sub>CHCH<sub>2</sub>), 7.03-7.07 (m, 4H, Ar), 7.21-7.26 (m, 6H, Ar).

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  28.2 (*t*-Bu), 39.10 (PhCH<sub>2</sub>CH), 51.2 (CHNH), 51.5 (NCH<sub>2</sub>CH), 51.8 (NCH<sub>2</sub>Ph), 80.1 (C(CH<sub>3</sub>)<sub>3</sub>), 108.0 (m, C-F), 117.7 (CHCH<sub>2</sub>), 127.0, 127.2, 127.3, 128.4, 128.6, 129.2 (Ar), 132.6 (CHCH<sub>2</sub>), 135.7-139.7 (m, C-F), 136.4, 136.7 (Ar), 141.2-144.7, 142.9-146.4 (m, C-F), 155.1 (OCO), 158.0 (OCO), 165.2 (C=N);  $[\alpha]_{\text{D}}^{20}$  -1.4 (*c* 1.3 CHCl<sub>3</sub>).

TOF MS ES<sup>+</sup>[MH]<sup>+</sup>: Found: 604.2239; Calcd for C<sub>31</sub>H<sub>31</sub>F<sub>5</sub>N<sub>3</sub>O<sub>4</sub>: 604.2235.

**(*E*)-(*S*)-*tert*-Butyl (1-allyl(benzyl)amino)-1-{[(pentafluorobenzoyl)-oxy]imino}propan-2-yl-carbamate (**4.21b**)**



A mixture of (*E/Z*)-**4.18b** (3:1, 400 mg, 2.12 mmol), NCS (286 mg, 2.14 mmol) and *N*-allyl benzyl amine (312 mg, 2.12 mmol) in dry DMF (10 mL) were reacted according to general method E and the crude residue (isomer ratio 8:3 based on analysis of  $^1\text{H}$  NMR spectrum) was subjected to flash column chromatography (PE/EA = 9/1-17/3) to give **4.20b** as a single isomer (210, mg, 30%), which was not purified further.

Selected data for **4.20b**.

TOF MS ES<sup>+</sup>[MH]<sup>+</sup>: Calcd for C<sub>18</sub>H<sub>28</sub>N<sub>3</sub>O<sub>3</sub>: 334.2131, Found: 334.2021.

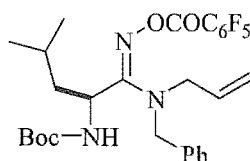
A sample of (*E/Z*)-**4.20b** (170 mg), TEA (80  $\mu$ L, 0.54 mmol) and  $\text{C}_6\text{F}_5\text{COCl}$  (123mg, 0.54 mmol) in dry DCM (15 mL) was reacted as described in general procedure F, and the crude product purified by flash column chromatography (PE/EA = 97/3) to give 170 mg (63%) of (*E*)-**4.21b** as a viscous colorless oil.

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.41 (d,  $J$  = 7.5 Hz, 3H,  $\text{CH}_3\text{CH}$ ), 1.45 (s, *t*-Bu), 3.77 (dd,  $J$  = 17Hz, 5Hz, 1H,  $\text{NCH}_2\text{CH}$ ), 4.33 (m, 1H,  $\text{NCH}_2\text{CH}$ ), 4.38 (d,  $J$  = 16.5 Hz, 1H,  $\text{NCH}_A\text{Ph}$ ), 4.75-4.81 (m, 2H,  $\text{NCH}_B\text{Ph}$ ,  $\text{CH}_3\text{CH}_\alpha$ ), 5.18-5.22 (m, 2H,  $\text{CHCH}_2$ ), 5.36 (d,  $J$  = 9 Hz, 1H, NH), 5.81-5.89 (m, 1H,  $\text{CHCH}_2$ ), 7.22-7.32 (m, 5H, Ar).

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  18.6 ( $\text{CH}_3\text{CH}$ ), 28.2 (*t*-Bu), 45.2 ( $\text{CH}_\alpha$ ), 51.8 ( $\text{NCH}_2\text{CH}$ ), 52.2 ( $\text{NCH}_2\text{Ph}$ ), 80.0 ( $\text{C}(\text{CH}_3)_3$ ), 108.0 (m, C-F), 117.2 ( $\text{CHCH}_2$ ), 127.1, 127.2, 128.5 (Ar), 132.9 ( $\text{CHCH}_2$ ), 135.7-139.4 (m, C-F), 137.0 (Ar), 141.0-144.7, 142.8-146.3, (m, C-F), 155.2 (OCO), 157.2 (OCO), 166.8 (C=N);  $[\alpha]^{20}_{\text{D}} +33.2$  (*c* 1.0  $\text{CHCl}_3$ ).

TOF MS  $\text{ES}^+ [\text{MH}]^+$ : Found: 528.1944; Calcd for  $\text{C}_{25}\text{H}_{27}\text{F}_5\text{N}_3\text{O}_4$  528.1922.

**(*E*)-(*S*)- *tert*-Butyl(1-allyl(benzyl)amino)-1-[[pentafluorobenzoyl]-oxy]imino}-4-methyl pentan-2-yl-carbamate (**4.21c**)**



A mixture of (*E/Z*)-**4.18c** (3:2, 600 mg, 2.79 mmol), NCS (372 mg, 2.79 mmol) and *N*-allyl benzyl amine (414 mg, 2.81 mmol) in dry DMF (10 mL) were reacted according to general method E and the crude residue (isomer ratio 11:1 based on analysis of  $^1\text{H}$  NMR spectrum) was subjected to flash column chromatography (PE/EA = 9/1-17/3) to give 180 mg (20%) of (*E/Z*)-**4.20c** as yellow gum (5:1 determined by analysis of  $^1\text{H}$  NMR spectrum), that was not purified further.

Selected data for **4.20c**.

TOF MS ES<sup>+</sup>[MH]<sup>+</sup>: Calcd for C<sub>21</sub>H<sub>34</sub>N<sub>3</sub>O<sub>3</sub>: 376.2600, Found: 376.2558.

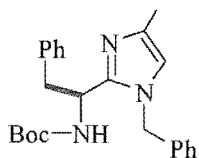
A sample of (*E/Z*)-**4.20c** (150 mg), TEA (64  $\mu$ L, 0.46 mmol) and C<sub>6</sub>F<sub>5</sub>COCl (106mg, 0.46 mmol) in dry DCM (15 mL) was reacted as described in general procedure F, and the crude product purified by flash column chromatography (PE/EA = 97/3) to give 40% of recovered starting material **4.20c** and 75 mg (31%) of (*E*)-**4.21c** as a colorless oil.

<sup>1</sup>H NMR (500 MHz)  $\delta$  0.72 (d, *J* = 6.5 Hz, 3H, CH<sub>3</sub>), 0.86 (d, *J* = 6.5 Hz, 3H, CH<sub>3</sub>), 0.93-1.01 (m, 1H, (CH<sub>3</sub>)<sub>2</sub>CH), 1.45 (s, *t*-Bu), 1.59-1.65 (m, 1H, CHCH<sub>2</sub>CH), 1.87-1.93 (m, 1H, CHCH<sub>2</sub>CH), 3.80 (dd, *J* = 16.5 Hz, 5 Hz, 1H, NCH<sub>2</sub>CH), 4.28 (dd, *J* = 17 Hz, 4 Hz, 1H, NCH<sub>2</sub>CH), 4.41 (d, *J* = 16.5 Hz, 1H, NCH<sub>A</sub>Ph), 4.61-4.72 (m, 1H, CH), 4.75 (d, *J* = 16.5 Hz, 1H, NCH<sub>B</sub>Ph), 5.17-5.25 (m, 2H, CHCH<sub>2</sub>), 5.25 (d, *J* = 9.5 Hz, 1H, NH), 5.81-5.88 (m, 1H, CHCH<sub>2</sub>), 7.20-7.32 (m, 5 H, Ar).

<sup>13</sup>C NMR (75 MHz)  $\delta$  21.2 (CH<sub>3</sub>CH), 23.2 (CH<sub>3</sub>CH), 25.1 ((CH<sub>3</sub>)<sub>2</sub>CH), 28.2 (*t*-Bu), 41.3 (CHCH<sub>a</sub>), 48.3 (CH<sub>a</sub>), 51.8 (NCH<sub>2</sub>CH), 52.1 (NCH<sub>2</sub>Ph), 79.9 ((CH<sub>3</sub>)<sub>3</sub>C), 117.5 (CHCH<sub>2</sub>), 127.1, 127.2, 128.5 (Ar), 132.7 (NCH<sub>2</sub>CHCH<sub>2</sub>), 135.6-139.5 (m, C-F), 137.0 (Ar), 140.9-144.9 (m, C-F), 142.5-146.4 (m, C-F) 155.5 (OCO), 157.2 (OCO), 166.8 (C=N); [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 59.8 (*c* 2.0 CHCl<sub>3</sub>).

TOF MS ES<sup>+</sup>[M + Na]<sup>+</sup>: Found: 592.1835; Calcd for C<sub>28</sub>H<sub>32</sub>F<sub>5</sub>N<sub>3</sub>NaO<sub>4</sub>: 592.2211.

(*S*)- *tert*-Butyl-1-(1-benzyl-4-methyl-1*H*-imidazol-2-yl)-2-phenylethyl carbamate (**4.22a**)



A mixture of (*E*)-**4.21a** (100 mg, 0.17 mmol), TEA (120  $\mu$ L, 0.83 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (19 mg, 0.017 mmol) in dry DMF (4 mL) was treated as described in general procedure G with

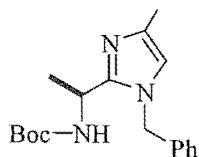
heating at 80 °C for 30 min. The residue was purified by flash column chromatography (PE/EA = 60/40-20/80) to give 45 mg (70%) of **4.22a** as a yellow solid.

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.36 (s, 9H, *t*-Bu), 2.20 (s, 3H, CH<sub>3</sub>), 3.12-3.22 (m, 2H, PhCH<sub>2</sub>CH), 4.67 (m, 2H, NCH<sub>2</sub>Ph), 4.95 (m, 1H, CH), 5.44 (bd,  $J$  = 8.5 Hz, 1H, NH), 6.35 (bs, 1H, CHN), 6.88 (m, 2H, Ar), 7.02 (d,  $J$  = 5.4 Hz, 2H, Ar), 7.19-7.23 (m, 6H, Ar).

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  13.6 (CH<sub>3</sub>CCHN), 28.3 (3 CH<sub>3</sub>, *t*-Bu), 42.0 (PhCH<sub>2</sub>CH), 48.0 (CH<sub>2</sub>CH), 48.9 (PhCH<sub>2</sub>N), 79.4 (C(CH<sub>3</sub>)<sub>3</sub>), 115.9 (CH<sub>3</sub>CCH), 126.5, 127.2, 127.8, 129.3, 128.7, 129.5, 136.3, 136.7 (Ar), 137.4 (CH<sub>3</sub>CCH), 147.0 (OCO), 155.0 (C=N);  $[\alpha]^{20}_{\text{D}}$  -8.3 (c 1.0 CHCl<sub>3</sub>).

TOF MS ES<sup>+</sup>[MH]<sup>+</sup>: Found: 392.2330; Calcd for C<sub>24</sub>H<sub>30</sub>N<sub>3</sub>O<sub>2</sub>: 392.2338.

**(*S*)-*tert*-Butyl-1-(1-benzyl-4-methyl-1*H*-imidazol-2-yl)ethyl carbamate (**4.22b**)**



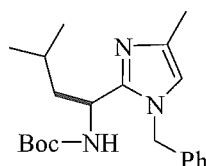
A mixture of (*E*)-**4.21b** (110 mg, 0.21 mmol), TEA (145  $\mu\text{L}$ , 1.09 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (24 mg, 0.021 mmol) in dry DMF (6 mL) was treated as described in general procedure G with heating at 80 °C for 1 h. The residue was purified by flash column chromatography (EA/PE = 70/30) to give 42 mg (68%) of **4.22b** as a yellow solid.

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.39 (s, 9H, *t*-Bu), 1.43 (d,  $J$  = 7 Hz, 3H, CH<sub>3</sub>CH), 2.19 (d,  $J$  = 1 Hz, 3H, CH<sub>3</sub>), 4.88-4.94 (m, 1H, CH<sub>3</sub>CH <sub>$\alpha$</sub> ), 5.08 (d,  $J$  = 16 Hz, 1H, NCH<sub>A</sub>Ph), 5.16 (d,  $J$  = 16 Hz, 1H, NCH<sub>B</sub>Ph), 5.27 (bd,  $J$  = 8.5 Hz, 1H, CHNH), 6.52 (s, 1H, CHN), 7.10 (d,  $J$  = 7.5 Hz, 2H, Ar), 7.28 (d,  $J$  = 7 Hz, 1H, Ar), 7.32 (t,  $J$  = 7.5, 2H, Ar).

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  13.5 (CH<sub>3</sub>CCHN), 20.9 (CH<sub>3</sub>CH), 28.3 (3 CH<sub>3</sub>, *t*-Bu), 41.9 (CH<sub>3</sub>CHNH), 49.1 (PhCH<sub>2</sub>N), 79.4 (C(CH<sub>3</sub>)<sub>3</sub>), 116.5 (CH<sub>3</sub>CCH), 126.8, 127.8, 128.8, 136.4 (CH<sub>3</sub>CCH), 136.7 (Ar), 148.2 (OCO), 154.9 (C=N);  $[\alpha]^{20}_{\text{D}}$  -72.4 (c 1.0 CHCl<sub>3</sub>).

TOF MS ES<sup>+</sup>[MH]<sup>+</sup>: Found: 316.2063; Calcd for C<sub>18</sub>H<sub>26</sub>N<sub>3</sub>O<sub>2</sub>: 316.2025.

**(*S*)-*tert*-Butyl-1-(1-benzyl-4-methyl-1*H*-imidazol-2-yl)-3-methyl butyl carbamate (4.22c)**



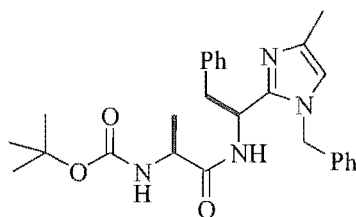
A mixture of (*E*)-**4.21c** (51 mg, 0.09 mmol), triethylamine (62  $\mu$ L, 0.44 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (10 mg, 0.009 mmol) in dry DMF (6 mL) was treated as described in general procedure G with heating at 80 °C for 1 h. The residue was purified by flash column chromatography (PE/EA = 70/30-30/70) to give 18 mg (56%) of **4.22c** as a thick oil.

<sup>1</sup>H NMR (500 MHz)  $\delta$  0.78 (m, 6H, 2 CH<sub>3</sub>), 1.38 (s, 9H, *t*-Bu), 1.52-1.56 (m, 2H, CH<sub>2</sub>CH), 1.81 (t, *J* = 14.5 Hz, 1H, CH<sub>2</sub>CH), 2.19 (d, *J* = 1.5 Hz, 3H, CH<sub>3</sub>), 4.83-4.88 (m, 1H, CH), 5.04-5.25 (m, 3H, NH, NCH<sub>2</sub>Ph), 6.52 (s, 1H, CH<sub>3</sub>CCHN), 7.13 (d, *J* = 10 Hz, 2H, Ar), 7.27-7.35 (m, 3H, Ar).

<sup>13</sup>C NMR (75 MHz)  $\delta$  13.6 (CH<sub>3</sub>CCHN), 21.9 (CH<sub>3</sub>CH), 22.8 (CH<sub>3</sub>CH), 24.60 ((CH<sub>3</sub>)<sub>2</sub>CH), 28.3 (*t*-Bu), 43.8 (CH<sub>2</sub>CHNH), 44.0 (CH<sub>2</sub>CHNH) 49.1 (PhCH<sub>2</sub>N), 79.3 (C(CH<sub>3</sub>)<sub>3</sub>), 116.3 (CH<sub>3</sub>CCHN), 127.0, 127.8, 128.8 (Ar), 136.5 (CH<sub>3</sub>CCHN), 136.9 (Ar), 148.4 (OCO), 155.2 (C=N); [ $\alpha$ ]<sub>D</sub><sup>20</sup> -54.3 (*c* 1.0 CHCl<sub>3</sub>).

TOF MS ES<sup>+</sup>[MH]<sup>+</sup>: Found: 358.2596; Calcd for C<sub>21</sub>H<sub>32</sub>N<sub>3</sub>O<sub>2</sub>: 358.2495.

**(*S*)-*tert*-Butyl-*N*-[1-(1-benzyl-4-methyl-1*H*-imidazole-2-yl)-2(*S*)-phenylethyl]alaninate (4.24)**



Compound **4.22a** (20 mg, 0.05 mmol) was reacted with 1N HCl (aq, 1 mL) in ethyl acetate (3 mL) at rt with stirring for 3 h. The progress of the reaction was monitored by TLC. EA was evaporated in vacuo, MeOH was added ( $\times 2$ ) and the solvent was evaporated in vacuo. The crude free amine **4.23** was dried in vacuo and used without further purification.

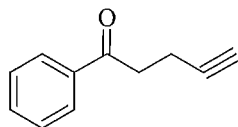
(*S*)-*N*,*t*-Boc alanine (9.7 mg, 0.05 mmol) was added to the crude free amine (15 mg, 0.05 mmol), EDCI (10 mg, 0.05 mmol), HOBT (14 mg, 0.10 mmol) and DIPEA (180  $\mu$ L) in dry DMF (6 mL) and the mixture was stirred at rt for 16 h. Water (2 mL) and EA (4 mL) were added to the mixture, organic phase separated and the aq. phase extracted with EA ( $\times 3$ ). The combined organic fractions were washed successively with H<sub>2</sub>O ( $\times 2$ ), NaHCO<sub>3</sub>, brine, dried (MgSO<sub>4</sub>) and evaporated in vacuo. The residue (a single diastereoisomer determined by analysis of <sup>1</sup>H NMR spectrum) was purified by flash column chromatography (PE/EA = 50:50 then 70:30) to give **4.24** (12 mg, 52%) as a clear oil.

<sup>1</sup>H NMR (500 MHz)  $\delta$  1.20 (d,  $J$  = 7.5 Hz, 1H, CH<sub>3</sub>CH), 1.41 (s, 9H, *t*-Bu), 2.19 (s, 3H, CH<sub>3</sub>), 3.11-3.15 (m, 1H, PhCH<sub>A</sub>CH <sub>$\alpha$</sub> ), 3.20 (dd,  $J$  = 13.5 Hz, 7 Hz, 1H, PhCH<sub>B</sub>CH), 4.08 (bs, 1H, CH<sub>3</sub>CH), 4.66-4.75 (m, 3H, NCH<sub>2</sub>Ph, NH), 4.89 (bm, 1H, NH), 5.26 (dd,  $J$  = 15.5 Hz, 8.5 Hz, 1H, PhCH<sub>2</sub>CH), 6.37 (s, 1H, CHN), 6.88 (t,  $J$  = 3.5 Hz, 2H, Ar), 7.01 (m, 3H, Ar), 7.19-7.27 (m, 2H, Ar).

<sup>13</sup>C NMR (75 MHz)  $\delta$  13.4 (CH<sub>3</sub>CCH), 18.3 (CH<sub>3</sub>CH), 28.2 (*t*-Bu), 41.2 (PhCH<sub>2</sub>CH), 46.4 (CH <sub>$\alpha$</sub> ), 48.9 (NCH<sub>2</sub>Ph), 50.2 (CH<sub>3</sub>CH <sub>$\alpha$</sub> ), 80.0 (C(CH<sub>3</sub>)<sub>3</sub>), 116.2 (CHN), 126.6, 127.0, 127.8, 128.3, 128.8, 129.4, 136.2, 136.6 (Ar), 137.1 (CCHN), 146.3 (OCO), 155.1 (C=N), 171.7 (NHCOCH); TOF MS ES<sup>+</sup>[MH]<sup>+</sup>: Found: 463.2760; Calcd for C<sub>27</sub>H<sub>35</sub>N<sub>4</sub>O<sub>3</sub>: 463.2709.

## 8.5 Experimental Work Described in Chapter Five

### 1-Phenylpent-4-yn-1-one (5.32)

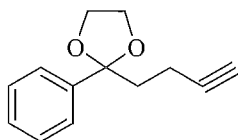


Acetophenone *N,N*-dimethyl hydrazone<sup>6</sup> (2.0 g, 12.32 mmol) was treated with freshly prepared LDA [from *n*-BuLi (1.6 M in hexane, 7.7 mL) and *N,N*-diisopropylamine (2.6 mL) in THF (25 mL)] at 0 °C and stirred for 1 h under argon atmosphere. 4-Bromo-1-butyne **5.31** (0.92 mL) in THF (4mL) was added according to general procedure H. The crude alkylated hydrazone was then hydrolyzed by adding acetic acid (5.9 mL, 104 mmol), sodium acetate (2.83 g, 20.85 mmol), water (0.7 mL), and THF (3.3 mL) were added and the mixture was stirred at rt for five hours. After work up, the crude product was purified by flash column chromatography (H/EA = 93/7) to give 1.1 g (91%) of **5.32** as a yellow oil. <sup>1</sup>H NMR (500 MHz) δ 1.99 (t, *J* = 2.5 Hz, 1H, C≡CH), 2.63 (dt, *J* = 8 Hz, 3 Hz, 2H, CH<sub>2</sub>C≡CH), 3.24 (t, *J* = 7.5 Hz, ,CH<sub>2</sub>CH<sub>2</sub>C≡CH), 7.45 (t, *J* = 8 Hz, 2H, Ar), 7.57-7.59 (m, 1H, Ar), 7.96 (d, *J* = 8 Hz, 2H, Ar).

<sup>13</sup>C NMR (75 MHz) δ 13.1 (CH<sub>2</sub>C≡CH), 37.4 (CH<sub>2</sub>CH<sub>2</sub>C≡CH), 68.7 (C≡CH), 83.3 (C≡CH), 127.9, 128.6, 133.2, 136.4 (Ar), 197.5 (C=O).

Micro. Found: C, 83.32; H, 6.49%. Calcd for C<sub>13</sub>H<sub>10</sub>O: C, 83.51; H, 6.37%

### 2-But-3-yn-1-yl-2-phenyl-1,3-dioxolane (5.33)<sup>21</sup>





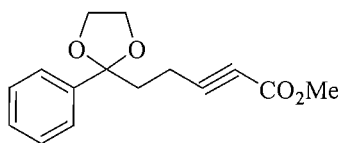
A solution of the ketone **5.32** (1.90 g, 12.04 mmol) in benzene, ethylene glycol (2.5 mL, 45.17 mmol) and a catalytic amount of *p*-TsOH were refluxed for 3 h using a Dean-Stark apparatus for removal of water. The reaction was quenched by adding sat. NaHCO<sub>3</sub> soln (aq.), extracted with EA (×3), washed with brine, dried over MgSO<sub>4</sub> and evaporated in vacuo. The crude product was purified by recrystallization from n-hexane to give 2.3 g (95%) of **5.33** as a colorless solid.

<sup>1</sup>H NMR (500 MHz) δ 1.89 (t, *J* = 2.5 Hz, 1H, C≡CH), 2.14-2.17 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>C≡CH), 2.27-2.30 (m, 2H, HC≡CCH<sub>2</sub>), 3.77 (t, *J* = 7 Hz, 2H, CH<sub>2</sub>O), 4.01 (t, *J* = 7 Hz, 2H, CH<sub>2</sub>O), 7.28-7.31 (m, 1H, Ar), 7.34 (t, *J* = 7.5 Hz, 2H, Ar), 7.43-7.45 (m, 2H, Ar).

<sup>13</sup>C NMR (75 MHz) δ 13.1 (CH<sub>2</sub>C≡CH), 39.3 (CH<sub>2</sub>CH<sub>2</sub>C≡CH), 64.6 (OCH<sub>2</sub>CH<sub>2</sub>O), 67.8 (C≡CH), 84.1 (C≡CH), 109.3 (PhCOO), 125.9, 128.01, 128.2, 141.9 (Ar).

Micro. Found: C, 76.91; H, 7.05%. Calcd for C<sub>13</sub>H<sub>14</sub>O<sub>2</sub>: C, 77.20; H, 6.97%

#### Methyl 5-(2-phenyl-1,3-dioxolan-2-yl)pent-2-ynoate (**5.34**)

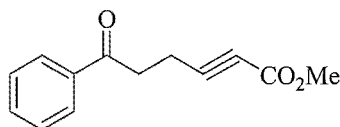


*n*-Butyl lithium (1.6 M in hexane, 2.2 mL) was added to a solution of **5.33** (684 mg, 3.38 mmol) in THF (15 mL) at -78 °C and stirred for 1 h at the same temperature. Methyl chloroformate (0.05 mL, 4.06 mmol) in THF (5 mL) was added to the reaction mixture and stirred for 1 h. The reaction was stopped by adding NH<sub>4</sub>Cl (sat.), extracted with Et<sub>2</sub>O (×3), washed with H<sub>2</sub>O (×2), brine (×2), dried (MgSO<sub>4</sub>) and evaporated in vacuo. The crude product was purified by flash column chromatography (H/EA = 90/10) to give 780 mg (88%) of **5.34** as a cream solid.

<sup>1</sup>H NMR δ 2.18 (t, *J* = 7.5 Hz, 2H, CHCH<sub>2</sub>), 2.43 (t, *J* = 7.7 Hz, 2H, CCH<sub>2</sub>), 3.73 (s, 3H, CH<sub>3</sub>), 3.78 (ddd, *J* = 7.3 Hz, 6.0 Hz, 3.4 Hz, 2H, CH<sub>2</sub>O), 4.01 (ddd, *J* = 7.4 Hz, 6.1 Hz, 3.6 Hz, 2H, CH<sub>2</sub>O), 7.28-7.36 (m, 3H, Ar), 7.42-7.44 (m, 2H, Ar).

$^{13}\text{C}$  NMR  $\delta$  13.4 ( $\text{C}\equiv\text{CCH}_2$ ), 38.1 ( $\text{C}\equiv\text{CCH}_2\text{CH}_2$ ), 52.5 ( $\text{CO}_2\text{CH}_3$ ), 64.7 ( $\text{OCH}_2\text{CH}_2\text{O}$ ), 72.6 ( $\text{C}\equiv\text{CCO}_2\text{CH}_3$ ) 89.4 ( $\text{C}\equiv\text{CCO}_2\text{CH}_3$ ), 109.0 ( $\text{PhCO}_2$ ), 125.7, 128.2, 128.3, 141.6 (Ar), 154.2 ( $\text{CO}_2\text{CH}_3$ ).

**Methyl 6-oxo-6-phenylhex-2-ynoate (5.35)**



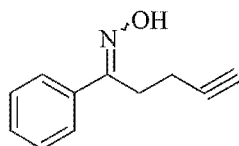
A solution of **5.34** (730 mg, 2.80 mmol) in THF (15 mL) and 1 N HCl (aq. 10 mL) was stirred at 40 °C for 4.5 h.  $\text{NaHCO}_3$  soln. (sat) was added to the mixture, extracted with  $\text{Et}_2\text{O}$  ( $\times 3$ ), washed with  $\text{H}_2\text{O}$  ( $\times 2$ ), brine ( $\times 1$ ), dried ( $\text{MgSO}_4$ ) and evaporated in vacuo. The crude product was purified by column chromatography (H/EA 90/10) to give 513 mg (84%) of **5.35** as a white solid.

$^1\text{H}$  NMR (500 MHz)  $\delta$  2.79 (t,  $J = 7.5$  Hz, 2H,  $\text{COCH}_2\text{CH}_2$ ), 3.31 (t,  $J = 7.5$  Hz, 2H,  $\text{COCH}_2\text{CH}_2$ ), 3.76 (s, 3H,  $\text{CH}_3$ ), 7.49 (t,  $J = 7.5$ , 2H, Ar), 7.59 (t,  $J = 7.4$ , 1H, Ar), 7.96 (d,  $J = 7.4$  Hz, 2H, Ar).

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  13.3 ( $\text{C}\equiv\text{CCH}_2$ ), 36.5 ( $\text{C}\equiv\text{CCH}_2\text{CH}_2$ ), 52.6 ( $\text{CO}_2\text{CH}_3$ ), 73.1 ( $\text{C}\equiv\text{CCO}_2\text{CH}_3$ ), 88.3 ( $\text{C}\equiv\text{CCO}_2\text{CH}_3$ ), 128.0, 128.7, 133.5, 136.1 (Ar), 154.0 ( $\text{CO}_2\text{CH}_3$ ), 196.7 (PhCO).

Micro. Found: C, 72.13; H, 5.61%. Calcd for  $\text{C}_{13}\text{H}_{12}\text{O}_3$ : C, 72.20; H, 5.59%.

**(*EZ*)-1-Phenylpent-4-yn-1-one oxime (5.36)**



The aryl alkynyl ketone **5.32** (1.09 g, 6.90 mmol), hydroxylamine hydrochloride (1.19 g, 13.8 mmol) and pyridine (1.56 mL, 19.32 mmol) were stirred in EtOH (30 mL) at rt for 2 h according to general procedure B. The crude oxime (5:2, based on analysis of  $^1\text{H}$  NMR spectrum) mixture was purified by column chromatography using (H/EA = 92/8) to elute 997 mg (83%) of *E*-**5.36** as a white solid first, and then 147 mg (12%) of *Z*-**5.36** as a yellow solid, thus yielding the oxime in a combined yield of 95%.

Data for (*E*)-**5.36**

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.98 (t,  $J$  = 3.0 Hz, 1H,  $\text{C}\equiv\text{CH}$ ), 2.53 (dt,  $J$  = 7.5, 2.5 Hz, 2H,  $\text{CH}_2\text{C}\equiv\text{CH}$ ), 3.06 (t,  $J$  = 7.5 Hz, 2H,  $\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$ ), 7.39-7.40 (m, 3H, Ar), 7.63-7.64 (m, 2H, Ar).

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  15.4 ( $\text{CH}_2\text{C}\equiv\text{CH}$ ), 25.8 ( $\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$ ), 69.1 ( $\text{C}\equiv\text{CH}$ ), 83.1 ( $\text{C}\equiv\text{CH}$ ), 126.4, 128.6, 129.4, 135.1 (Ar), 157.9 ( $\text{C}=\text{N}$ ).

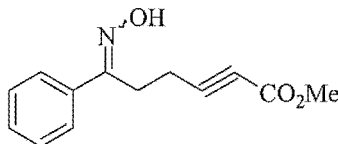
Micro. Found: C, 76.26; H, 6.39; N, 7.98%. Calcd for  $\text{C}_{11}\text{H}_{11}\text{NO}$ : C, 76.27; H, 6.4; N, 8.08%.

Data for (*Z*)-**5.36**

$^1\text{H}$  NMR (300 MHz)  $\delta$  1.98 (t,  $J$  = 3.0 Hz, 1H,  $\text{C}\equiv\text{CH}$ ), 2.37 (dt,  $J$  = 7.5, 3 Hz, 2H,  $\text{CH}_2\text{C}\equiv\text{CH}$ ), 2.78 (t,  $J$  = 7.5 Hz, 2H,  $\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$ ), 7.37-7.70 (m, 5H, Ar), 8.06 (bs, 1H,  $\text{C}=\text{NOH}$ ).

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  16.0 ( $\text{CH}_2\text{C}\equiv\text{CH}$ ), 34.4 ( $\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$ ), 69.4 ( $\text{C}\equiv\text{CH}$ ), 82.7 ( $\text{C}\equiv\text{CH}$ ), 127.7, 128.3, 129.1, 132.6 (Ar), 156.7 ( $\text{C}=\text{N}$ ).

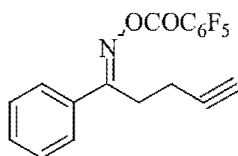
**(*E*)-Methyl-6-(hydroxyimino)-6-phenylhex-2-ynoate (5.37)**



The aryl alkynyl ketone **5.35** (590 mg, 2.73 mmol), hydroxylamine hydrochloride (402 mg, 6.8 mmol) and pyridine (610  $\mu$ L, 7.6 mmol) were stirred in EtOH (30 mL) at rt for 5 h according to general procedure B. The crude oxime (single isomer, based on analysis of  $^1\text{H}$  NMR spectrum) mixture was purified by column chromatography using (H/EA = 90/10) to elute 441 mg (70%) of *E*-**5.37** as a white solid.

$^1\text{H}$  NMR (300 MHz)  $\delta$  2.66 (t,  $J$  = 7.9 Hz, 2H,  $\text{CH}_2\text{C}\equiv\text{CCO}_2$ ), 3.09 (t,  $J$  = 7.9 Hz, 2H,  $\text{CH}_2\text{CH}_2\text{C}\equiv\text{C}$ ), 3.75 (s, 3H,  $\text{CH}_3$ ), 7.36-7.43 (m, 2H, Ar), 7.58-7.65 (m, 2H, Ar), 8.10 (bs, 1H,  $\text{C}=\text{NOH}$ ).

**(*E*)-1-Phenylpent-4-yn-1-one *O*-pentafluorobenzoyl oxime (**5.38**)**



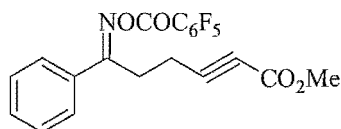
To a solution of *E*-**5.36** (640 mg, 3.69 mmol) and TEA (1.0 mL, 7.38 mmol) in DCM (20 mL) at 0 °C was added  $\text{C}_6\text{F}_5\text{COCl}$  (1.36 mg, 5.91 mmol) in DCM (5 mL) and stirred for 1.5 h according to general procedure C. The crude oxime was purified by silica chromatography (H/EA = 95/5) to give 1.16 g (88%) of *E*-**5.38** as a white solid.

Data for *E*-**5.38**.

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.99 (t,  $J$  = 2.5 Hz, 1H,  $\text{C}\equiv\text{CH}$ ), 2.50 (dt,  $J$  = 7.5, 2.5 Hz, 2H,  $\text{CH}_2\text{C}\equiv\text{CH}$ ), 3.15 (t,  $J$  = 7.5 Hz, 2H,  $\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$ ), 7.40 (t,  $J$  = 7.5 Hz, 2H, Ar), 7.49-7.52 (m, 1H, Ar), 7.77 (d,  $J$  = 8 Hz, 2H, Ar).

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  15.9 ( $\text{CH}_2\text{C}\equiv\text{CH}$ ), 27.6 ( $\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$ ), 69.9 ( $\text{C}\equiv\text{CH}$ ), 81.4 ( $\text{C}\equiv\text{CH}$ ), 107.0 (m, C-F), 127.4, 128.7, 131.2, 132.5 (Ar), 135.8-139.6 (m, C-F), 141.6-145.4, 143.6-147.4, (m, C-F), 156.2 ( $\text{OCOC}_6\text{F}_5$ ), 166.6 ( $\text{C}=\text{N}$ ).

TOF MS  $\text{ES}^+$   $[\text{MH}]^+$ : Found: 368.0637; Calcd for  $\text{C}_{18}\text{H}_{11}\text{F}_5\text{NO}_2$ : 368.0710.

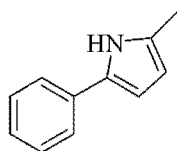
**(*E*)-Methyl-6-(pentafluorobenzoyloxyimino)-6-phenylhex-2-ynoate (5.39)**

To a solution of *E*-5.37 (292 mg, 1.26 mmol) and TEA (350  $\mu$ L, 2.53 mmol) in DCM (20 mL) at 0 °C was added  $C_6F_5COCl$  (554 mg, 2.40 mmol) in DCM (5 mL) and stirred for 1.5 h according to general procedure C. The crude oxime was purified by recrystallization (H/EA) to give 420 mg (75%) of *E*-3.39 as a white solid.

$^1H$  NMR (500 MHz)  $\delta$  2.64 (t,  $J = 7.5$  Hz, 2H,  $CH_2C\equiv CCO_2$ ), 3.21 (t,  $J = 7.5$  Hz, 2H,  $CH_2CH_2C\equiv C$ ), 3.72 (s, 3H,  $CH_3$ ), 7.46 (t,  $J = 7.5$ , 2H, Ar), 7.51 (t,  $J = 7.0$ , 1H, Ar), 7.76 (d,  $J = 7.5$  Hz, 2H, Ar).

$^{13}C$  NMR (75 MHz)  $\delta$  16.14 ( $CH_2C\equiv CCO_2$ ), 26.50 ( $CH_2CH_2C\equiv C$ ), 52.53 ( $CO_2CH_3$ ), 73.86 ( $C\equiv CCO_2CH_3$ ), 85.97 ( $C\equiv CCO_2CH_3$ ), 127.4, 128.9, 131.4, 132.1 (Ar), 135.8-136.3, 139.2-139.7, 141.7-142.2, 143.6-143.9, 145.0-145.6, 147.0-147.6 (m, C-F), 153.6 ( $CO_2CH_3$ ), 156.0 ( $CO_2C_6F_5$ ), 196.7 ( $C=N$ ).

Micro. Found: C, 56.41; H, 3.02; N, 3.33%. Calcd for  $C_{20}H_{12}NO_4F_5$ : C, 56.48; H, 2.84; N, 3.29%.

**2-methyl-5-phenyl-1*H*-pyrrole (5.40)<sup>22,23</sup>****a) Preparation via A-H reaction of 5.38**

$Pd(PPh_3)_4$  (31 mg, 0.027 mmol) was added to a solution of *E*-5.38 (100 mg, 0.27 mmol) and TEA (190  $\mu$ L, 1.3 mmol) in dry DMF (0.05 M) under argon atmosphere at rt and stirred at

80 °C for 1 h according to general procedure I. The residue was purified by preparative thin layer chromatography (H/EA = 8/2) to give 14.7 mg (35%) of **5.40** as a dark red oil.

<sup>1</sup>H NMR (500 MHz) δ 3.33 (s, 3H, CH<sub>3</sub>), 5.94 (bs, 1H, CH<sub>3</sub>CCH), 6.39 (t, *J* = 3 Hz, PhCCH, 1H), 7.15 (t, *J* = 7.4 Hz, 1H, Ar), 7.34 (t, *J* = 8 Hz, 2H, Ar), 7.43 (d, *J* = 7.8 Hz, 2H, Ar), 8.09 (bs, 1H, NH).

<sup>13</sup>C NMR (125 MHz) δ 13.2, 106.1, 107.9, 123.3, 125.6, 128.8, 129.0, 130.5, 141.7.

**b) Preparation via A-H reaction followed by Transmetallation with PhSnBu<sub>3</sub>**

Pd(PPh<sub>3</sub>)<sub>4</sub> (30.5 mg, 0.026 mmol) was added to a solution of *E*-**5.38** (97 mg, 0.26 mmol), TEA (180 μL, 1.32 mmol) and PhSnBu<sub>3</sub> (170 μL, 0.53 mmol) in dry DMF or THF (0.05 M) at rt and stirred at 70 °C for 11 h according to general procedure J. The residue was purified by preparative thin layer chromatography (H/EA = 85/15) to give 3 mg (7%) of **5.40** as a dark red oil.

Data for **5.40** as above.

**c) Preparation via A-H reaction followed by Intermolecular Heck Reaction with methyl acrylate**

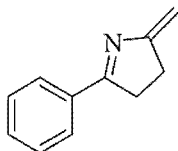
Pd(PPh<sub>3</sub>)<sub>4</sub> (39 mg, 0.034 mmol) was added to a solution of *E*-**5.38** (124 mg, 0.34 mmol), TEA (230 μL, 1.69 mmol) and methyl acrylate (60 μL, 0.68 mmol) in dry DMF (0.05 M) at rt and stirred at 80 °C for 5 h according to general procedure K. The residue was purified by preparative thin layer chromatography (H/EA = 83/17) to give 1.5 mg (6%) of **5.40** as a dark red oil.

Data for **5.40** as above.

**d) Preparation via A-H reaction followed by Carbonylation/Nucleophile Insertion**

$\text{Pd}(\text{PPh}_3)_4$  (38 mg, 0.033 mmol) was added to a solution of *E*-**5.38** (122 mg, 0.33 mmol) TEA (230  $\mu\text{L}$ , 1.65 mmol) and  $\text{C}_2\text{H}_5\text{OH}$  (90  $\mu\text{L}$ , 1.65 mmol) in dry DMF (0.05 M) at rt and stirred at 80 °C for 5 h according to general procedure L. The residue was purified by preparative thin layer chromatography (H/EA = 82/20) to give 3 mg (6%) of **5.40** as a dark red oil as well as 20 mg (26%) of **5.42**.

Data for **5.40** as above.

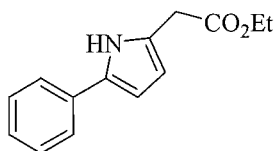
**2-Methylene-5-phenyl-3,4-dihydro-2H-pyrrole (**5.41**)**<sup>9,22</sup>

$\text{PhZnBr}$  (170  $\mu\text{L}$ , 0.53 mmol) was added over 20 min to a solution of *E*-**5.38** (144 mg, 0.40 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (46 mg, 0.04 mmol) in dry THF (0.05 M) at rt and stirred for 3 h according to the general procedure J. The residue was purified by preparative thin layer chromatography (H/EA = 98/2) to give 12 mg (28%) of **5.41** as a dark red oil as well as 21 mg of a mixture containing (16%) of **5.32** and (11%) of the starting material **5.38** determined by  $^1\text{H}$  NMR.

$^1\text{H}$  NMR (500 MHz)  $\delta$  2.63 (t,  $J$  = 7 Hz, 2H), 2.74 (t,  $J$  = 7 Hz, 2H), 4.16 (s, 1H), 4.62 (s, 1H), 7.39-7.41 (m, 3H), 7.65-7.69 (m, 2H).

**Ethyl (5-phenyl-1*H*-pyrrol-2-yl)acetate (5.42)**<sup>9,22,23</sup>

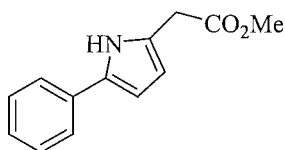
Preparation as for 5.40 (d) above.



<sup>1</sup>H NMR (500 MHz)  $\delta$  1.30 (t,  $J = 7.2$  Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 3.71 (s, 2H, CH<sub>2</sub>CO<sub>2</sub>), 4.20 (dd,  $J = 14.3$  Hz, 7.1 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 6.06 (t,  $J = 2.8$  Hz, 1H, CO<sub>2</sub>CH<sub>2</sub>CCH), 6.41 (t,  $J = 3$  Hz, PhCCH, 1H), 7.18 (t,  $J = 7.4$  Hz, 1H, Ar), 7.34 (t,  $J = 7.6$  Hz, 2H, Ar), 7.46 (d,  $J = 7.8$  Hz, 2H, Ar), 9.01 (bs, 1H, NH).

<sup>13</sup>C NMR (75 MHz)  $\delta$  14.2 (CH<sub>2</sub>CH<sub>3</sub>), 33.3 (CH<sub>2</sub>CH<sub>3</sub>), 61.2 (CH<sub>2</sub>CO<sub>2</sub>), 105.8 (NHCCH), 109.1 (CO<sub>2</sub>CCH), 123.6 (Ar), 124.5 (PhCCH), 126.0, 128.8 (Ar), 132.1 (CO<sub>2</sub>CH<sub>2</sub>CCH), 132.7 (Ar), 171.1 (CO).

TOF MS ES<sup>+</sup> [MH]<sup>+</sup>: Found: 230.1154; Calcd for C<sub>14</sub>H<sub>16</sub>NO<sub>2</sub>: 230.1181.

**Methyl (5-phenyl-1*H*-pyrrol-2-yl)acetate (5.43)**<sup>23</sup>

Pd(PPh<sub>3</sub>)<sub>4</sub> (27 mg, 0.023 mmol) was added to a solution of *E*-5.39 (100 mg, 0.23 mmol) and TEA (160  $\mu$ L, 1.17 mmol) in dry DMF (0.05 M) at rt and stirred at 80 °C for 2 h according to general procedure I. The residue was purified by preparative thin layer chromatography (H/EA = 82/20) to give 18.3 mg (37%) of 5.43.

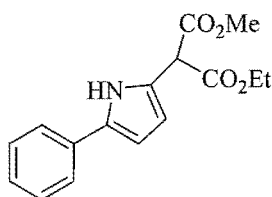
<sup>1</sup>H NMR (500 MHz)  $\delta$  3.71 (s, 2H, CH<sub>2</sub>CO<sub>2</sub>), 3.73 (s, 3H, CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 6.07 (t,  $J = 2.5$  Hz, 1H, CO<sub>2</sub>CH<sub>2</sub>CCH), 6.41 (t,  $J = 3.5$  Hz, 1H, PhCCH), 7.18 (t,  $J = 7.4$  Hz, 1H, Ar), 7.33 (t,  $J = 8$  Hz, 2H, Ar), 7.46 (dd,  $J = 8$  Hz, 1.5 Hz, 2H, Ar), 9.00 (bs, 1H, NH).



$^{13}\text{C}$  NMR (75 MHz)  $\delta$  33.1 ( $\text{CO}_2\text{CH}_3$ ), 52.2 ( $\text{CH}_2\text{CO}_2$ ), 105.8 ( $\text{NHCCH}$ ), 109.2 ( $\text{CO}_2\text{CCH}$ ), 123.6 (Ar), 124.3 ( $\text{PhCCH}$ ), 126.0, 128.8 (Ar), 132.2 ( $\text{CO}_2\text{CH}_2\text{CCH}$ ), 132.6 (Ar), 171.6 (CO).

TOF MS  $\text{ES}^+$   $[\text{MH}]^+$ : Found: 216.1125; Calcd for  $\text{C}_{13}\text{H}_{14}\text{NO}_2$ : 216.1025.

**Ethyl methyl (5-phenyl-1*H*-pyrrol-2-yl)malonate (5.45)**



$\text{Pd}(\text{PPh}_3)_4$  (32.6 mg, 0.028 mmol) was added to a solution of *E*-**5.38** (122 mg, 0.28 mmol), TEA (190  $\mu\text{L}$ , 1.41 mmol) and  $\text{C}_2\text{H}_5\text{OH}$  (80  $\mu\text{L}$ , 1.41 mmol) in dry DMF (0.05 M) at rt and stirred at 90  $^\circ\text{C}$  for 1 h according to the general procedure L. The residue was purified by preparative thin layer chromatography (H/EA = 85/15) to give 25 mg (52%) of a mixture as a dark red oil containing **5.45** as well as **5.43** (2:5, determined by analysis of  $^1\text{H}$  NMR spectrum).

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.30 (t,  $J = 7.2$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ), 3.78 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 4.20-4.27 (m, 2H,  $\text{CH}_2\text{CH}_3$ ), 4.78 (s, 1H,  $\text{CH}(\text{CO}_2\text{Me})\text{CO}_2\text{Et}$ ), 6.19 (t,  $J = 3$  Hz, 1H,  $\text{NHCCH}$ ), 6.43 (t,  $J = 3$  Hz, 1H,  $\text{PhCCH}$ ), 7.16-7.21 (m, 3H, Ar), 7.46-7.49 (m, 2H, Ar), 9.29 (bs, 1H, NH).

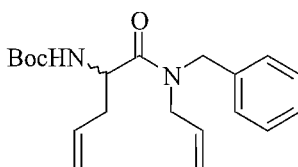
$^{13}\text{C}$  NMR (125 MHz)  $\delta$  13.9 ( $\text{CH}_2\text{CH}_3$ ), 50.9 ( $\text{CH}(\text{CO}_2\text{Me})\text{CO}_2\text{Et}$ ), 53.1 ( $\text{CO}_2\text{CH}_3$ ), 62.3 ( $\text{CH}_3\text{CH}_2\text{OCO}$ ), 105.8 ( $\text{PhCCH}$ ), 110.6 ( $\text{NHCCHCH}$ ), 123.9, 126.3, 128.8 (Ar), 132.5 ( $\text{CHCCH}$ ), 133.2 (Ar), 167.6, 168.1 (CO).

TOF MS  $\text{ES}^+$   $[\text{MH}]^+$ : Found: 288.1250; Calcd for  $\text{C}_{16}\text{H}_{18}\text{NO}_4$ : 288.1236.

## 8.6 Experimental Work Described in Chapter Seven

Acid<sup>24</sup> **7.37**, amine<sup>25</sup> **7.46**, and *N*-allyl benzyl amine<sup>8</sup> were prepared by literature methods.

### (±)-*tert*-Butyl (1-{{allyl(benzyl)amino}carbonyl}but-3-en-1-yl)carbamate (**7.29**)



EDCI (1.11g, 5.80 mmol), HOBT (1.57g, 11.61 mmol), and NMM (1.67 mL, 17.42 mmol) were added to a solution of (±) *N*-*t*-Boc allyl glycine (1.248g, 5.80 mmol) and *N*-allyl benzyl amine (795 mg, 5.80 mmol) in DMF (30 mL) under argon with stirring at rt for 16 h according to the general procedure M. The crude product (a 2:5 mixture of rotamers, based on analysis of <sup>1</sup>H NMR spectrum) was purified by flash column chromatography (PE/EA = 9/1 → 7/3) to give the 1.77g (88%) of the desired diene (±)-**7.29** as a cream solid.

Data for mixture (2:5)

FTIR (KBr): 3365, 2983, 2331, 1728, 1689, 1521, 1433, 1296, 1244, 1170, 1022, 912, 850, 786, 698.

<sup>1</sup>H NMR (500 MHz) δ 1.42 (s, 9H, *t*-Bu, minor), 1.44 (s, 9H, *t*-Bu, major), 2.31-2.42 (m, 3H, CHCH<sub>AB</sub>CHCH<sub>2</sub>, 2H, minor and CHCH<sub>A</sub>CHCH<sub>2</sub>, 1H, major), 2.43-2.54 (m, 1H, CHCH<sub>A</sub>CHCH<sub>2</sub>, major), 3.89 (dd, *J* = 18 Hz, 5 Hz, 2H, NCH<sub>AB</sub>CH, major), 3.97 (dd, *J* = 18 Hz, 6 Hz, 1.5 H, NCH<sub>AB</sub>CH, minor), 4.08 (dd, *J* = 16 Hz, 5.5 Hz, 0.5 H, NCH<sub>B</sub>CH, minor), 4.48 (d, *J* = 14.5 Hz, 1H, NCH<sub>A</sub>Ph, major), 4.61 (s, 2H, NCH<sub>AB</sub>Ph, minor), 4.64-4.68 (m, 1H, CHα, major), 4.71 (d, *J* = 15.5 Hz, 1H, NCH<sub>B</sub>Ph, major), 4.72-4.75 (m, 1H, CHα, minor), 5.07-5.21 (m, 4 H, NCH<sub>2</sub>CHCH<sub>2</sub>, CHCH<sub>2</sub>, minor & major), 5.67-5.81 (m, 2H, NCH<sub>2</sub>CHCH<sub>2</sub>, CHCH<sub>2</sub>, minor & major), 7.19-7.36 (m, 5H, Ar, minor & major).

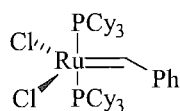
<sup>13</sup>C NMR (75 MHz) δ 28.3 (*t*-Bu), 37.7, 37.8 (CHCH<sub>2</sub>CH), 47.9 (NCH<sub>2</sub>CH), 48.2 (NCH<sub>2</sub>Ph), 49.03 (NCH<sub>2</sub>CH), 49.8, 49.9 (CHα), 50.05 (NCH<sub>2</sub>Ph), 79.5 (C(CH<sub>3</sub>)<sub>3</sub>), 117.6,

117.7 (CHCH<sub>2</sub>CHCH<sub>2</sub>), 118.57 (NCH<sub>2</sub>CHCH<sub>2</sub>), 126.8, 127.4, 127.7, 128.0, 128.5, 128.8 (Ar), 132.3, 132.5 (CHCH<sub>2</sub>CHCH<sub>2</sub>), 132.7, 132.8 (NCH<sub>2</sub>CHCH<sub>2</sub>), 136.2, 136.9 (Ar-C), 155.1, 155.2 (OCO*t*-Bu), 172.0, 172.2, (NCO).

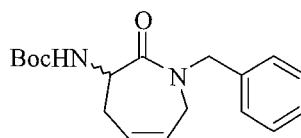
TOF MS ES<sup>+</sup> [MH]<sup>+</sup>: Found: 345.2178; Calcd for C<sub>20</sub>H<sub>29</sub>N<sub>2</sub>O<sub>3</sub>: 345.2178.

Anal found: C, 69.70; H, 8.15; N, 7.95%; calcd: C, 69.74; H, 8.19; N, 8.13%.

**(±)-*tert*-Butyl (1-benzyl-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-yl) carbamate (7.30)**



**6.2**



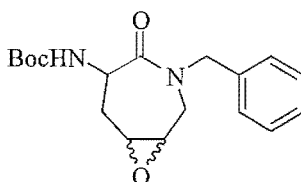
Catalyst **6.2** (16 mg, 0.02 mmol), dissolved in dry degassed DCM (3 mL) was added to a solution of the diene **7.29** (95 mg, 0.25 mmol), dissolved in dry degassed DCM (20 mL) under argon, according to the general procedure O. The mixture was refluxed for 24 h. The crude product was purified by flash column chromatography (PE/EA = 9/1 then 8/2) to give 66 mg (76%) of the desired olefinic lactam **7.30** as a brown solid.

FTIR (KBr): 3249, 2850, 2391, 1703, 1647, 1527, 1487, 1392, 1361, 1226, 1164, 1047, 1002, 968, 929, 798, 702, 626.

<sup>1</sup>H NMR (500 MHz) δ 1.38 (s, 9H, *t*-Bu), 2.20 (m, 1H, CHCH<sub>A</sub>CH), 2.60 (dd, *J* = 18 Hz, 4 Hz, 1H, CHCH<sub>B</sub>CH), 3.27 (dd, *J* = 7.5 Hz, 17.5 Hz, 1H, NCH<sub>A</sub>CH), 4.21 (td, *J* = 17.5 Hz, 3 Hz, 1H, NCH<sub>B</sub>CH), 4.53 (d, *J* = 15 Hz, 1H, NCH<sub>A</sub>Ph), 4.63 (d, *J* = 15 Hz, 1H, NCH<sub>B</sub>Ph), 4.86-4.91 (m, 1H, CHNH), 5.53 (m, 1H, CHCH<sub>2</sub>CHNH), 5.64 (m, 1H, CHCH<sub>2</sub>N), 5.82 (bd, *J* = 7 Hz, 1H, NH), 7.14 (d, *J* = 7 Hz, 2H, Ar), 7.17-7.24 (m, 3H, Ar).

<sup>13</sup>C NMR (75 MHz) δ 28.3 (*t*-Bu), 33.3 (CHCH<sub>2</sub>CH), 45.1 (NCH<sub>2</sub>CH), 49.94 (CHNH), 51.4 (NCH<sub>2</sub>Ph), 79.4 (C(CH<sub>3</sub>)<sub>3</sub>), 124.1 (CHCH<sub>2</sub>CHNH), 127.4, 127.7, 128.5 (Ar), 130.0 (CHCH<sub>2</sub>N), 136.7 (Ar), 154.9 (OCO *t*-Bu), 172.4 (NCO).

TOFMS ES<sup>+</sup> [MH]<sup>+</sup>: Found: 317.2242; Calcd for C<sub>18</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub>: 317.1856

**(±)-tert-Butyl (3-benzyl -4-oxo-8-oxa-3-azabicyco[5,1,0]oct-5-yl) carbamate (7.31)**

The olefinic lactam **7.30** (138 mg, 0.44 mmol) in acetone (12 mL) and water (10 mL) was treated with sodium hydrogen carbonate (1.24 g, 14.80 mmol) and Oxone® (2.68g, 4.35 mmol) as described in the general procedure P. The resulting crude epoxide was purified by column chromatography (PE/EA = 70:30) to give 91 mg (63%) of **7.31** (~1:1) as a white solid.

Data for mixture of diastereoisomers (~1:1)

FTIR (KBr): 2977, 2343, 1712, 1652, 1606, 1490, 1434, 1365, 1328, 1226, 1166, 1055, 1022, 977, 869, 742, 702.

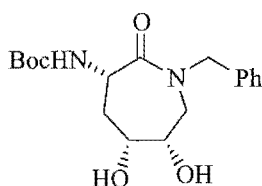
<sup>1</sup>H NMR (500 MHz) δ 1.45 (s, 9H), 1.91 (t, *J* = 12.5 Hz, 1H, CHCH<sub>A</sub>CH), 2.03 (t, *J* = 12.5 Hz, 1H, CHCH<sub>B</sub>CH), 2.52 (dddd, *J* = 11 Hz, 6.5 Hz, 4.5 Hz, 1H, CHCH<sub>A</sub>CH), 2.65 (d, *J* = 14.5 Hz, 1H, CHCH<sub>B</sub>CH), 2.90 (dd, *J* = 6 Hz, 11 Hz, 1H, OCHCH<sub>2</sub>N), 3.01 (m, 1H, OCHCH<sub>2</sub>CH), 3.04 (t, *J* = 4.5 Hz, 1H, OCHCH<sub>2</sub>N), 3.18 (t, *J* = 5.5 Hz, 1H, OCHCH<sub>2</sub>CH), 3.62 (dd, *J* = 4.5 Hz, 17 Hz, 2 H, CHCH<sub>AB</sub>N), 3.65 (d, *J* = 6.5 Hz, 1H, CHCH<sub>A</sub>N), 3.92 (d, *J* = 15.5 Hz, 1H, CHCH<sub>B</sub>N), 3.96 (d, *J* = 17 Hz, 1H, NCH<sub>A</sub>Ph), 4.33 (d, *J* = 14.5 Hz, 1H, NCH<sub>A</sub>Ph), 4.40-4.43 (m, 1H, NHCH), 4.55-4.59 (m, 1H, NHCH), 4.95 (d, *J* = 14.5 Hz, 1H, NCH<sub>B</sub>Ph), 5.27 (d, *J* = 15 Hz, 1H, NCH<sub>B</sub>Ph), 5.73 (bd, *J* = 7 Hz, 1H, NH), 5.86 (bd, *J* = 6.5 Hz, 1H, NH), 7.23 (t, *J* = 7.5 Hz, 2 H, Ar), 7.26-7.35 (m, 3H, Ar).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 28.2, 28.3, 30.4, 31.3, 44.2, 47.2, 47.7, 48.27, 50.0, 51.1, 51.2, 52.2, 52.4, 52.7, 127.6, 127.8, 128.0, 128.2, 128.6, 128.8, 136.2, 136.8, 154.9, 171.3, 172.2.

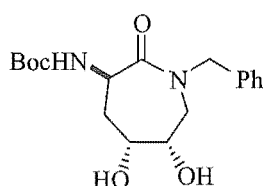
TOF MS ES<sup>+</sup> [MH]<sup>+</sup>: Found: 333.1811; Calcd for C<sub>18</sub>H<sub>25</sub>N<sub>2</sub>O<sub>4</sub>: 333.1814.

*tert*-Butyl [(3*S*,5*R*,6*S*)-1-benzyl-5,6-dihydroxy-2-oxoazepan-3-yl]carbamate (**7.32**)

and *tert*-butyl[(3*R*,5*R*,6*S*)-1-benzyl-5,6-dihydroxy-2-oxoazepan-3-yl]carbamate (**7.33**)



7.32



7.33

Potassium osmate (3 mg, 0.008 mmol), olefinic lactam **7.30** (52 mg, 0.16 mmol), *t*-butyl alcohol (3 mL), water (3 mL), potassium carbonate (68 mg, 0.49 mmol), potassium ferricyanide (162 mg, 0.49 mmol), ligand **7.21** or **7.22** (6.4 mg, 0.0016 mmol) and methane sulphonamide (31 mg, 0.33 mmol) were reacted according to the general method Q with stirring for 48 h. The crude product, obtained as a mixture (9:1 based on analysis of  $^1\text{H}$  NMR spectrum) was purified by flash column chromatography (PE/EA/acetone = 5:1:4) to give 41 mg (71%) of a mixture of diols **7.32** and **7.33**. Separation of the major isomer **7.32** was then achieved by recrystallisation ( $\text{CHCl}_3/\text{PE}$ ) to give the major isomer as a white solid. Further separation of **7.33** from the mixture could not be achieved.

Data for major isomer **7.32**

$^1\text{H}$ NMR major isomer ( $\text{CD}_3\text{CN}$ , 500 MHz)  $\delta$  1.23 (s, 9H, *t*-Bu), 1.53 (dd,  $J = 11.5$  Hz, 23.5 Hz, 1H,  $\text{CH}_\alpha\text{CH}_\text{A}\text{CHOH}$ ), 1.67 (dd,  $J = 12.5$  Hz, 4.0 Hz, 1H,  $\text{CH}_\alpha\text{CH}_\text{B}\text{CHOH}$ ), 2.94 (d,  $J = 4$  Hz, 1H,  $\text{NCH}_2\text{CHOH}$ ), 3.04 (d,  $J = 5.0$  Hz, 1H,  $\text{CHCH}_2\text{CHOH}$ ), 3.14 (dd,  $J = 15.5$  Hz, 6 Hz, 1H,  $\text{NCH}_\text{A}\text{CHOH}$ ), 3.23-3.26 (m, 1H,  $\text{NCH}_\text{B}\text{CHOH}$ ), 3.54 (bd, 1H,  $\text{CH}_\alpha\text{CH}_2\text{CHOH}$ ), 3.65 (bs, 1H,  $\text{NCH}_2\text{CHOH}$ ), 3.71 (d,  $J = 15.0$  Hz, 1H,  $\text{NCH}_\text{A}\text{Ph}$ ), 4.01-4.05 (m, 1H,  $\text{CH}_\alpha$ ), 5.16 (d,  $J = 15$  Hz, 1H,  $\text{NCH}_\text{B}\text{Ph}$ ), 5.72 (bs, 1H, NH), 7.03-7.08 (m, 3H, Ar), 7.12-7.14 (m, 2H, Ar).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  28.4 (*t*-Bu), 34.60 ( $\text{CH}_\alpha\text{CH}_2\text{CH}$ ), 46.93 ( $\text{NCH}_2\text{CH}$ ), 48.99 ( $\text{CH}_\alpha$ ), 53.14 ( $\text{NCH}_2\text{Ph}$ ), 68.41 ( $\text{CCH}_2\text{CHOH}$ ), 72.28 ( $\text{NCH}_2\text{CHOH}$ ), 79.87 ( $\text{C}(\text{CH}_3)_3$ ), 127.64, 128.08, 128.72, 136.90 (Ar), 155.22 (OCO), 171.63 (NCO).

Anal calcd: C, 61.52; H, 7.74; N, 7.9%. Found: C, 61.40; H, 7.43; N, 7.86%.

TOF MS  $\text{ES}^+$   $[\text{MH}]^+$ : Found: 351.1922; Calcd for  $\text{C}_{18}\text{H}_{27}\text{N}_2\text{O}_5$ : 351.1920.

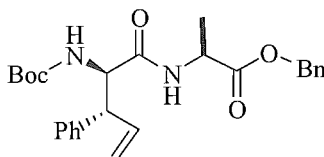
***tert*-Butyl [(3*R*,5*R*,6*S*)-1-benzyl-5,6-dihydroxy-2-oxoazepan-3-yl] carbamate (7.33)**

Data for minor isomer 7.33:

$^1\text{H}$ NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.44 (s, 9H, *t*-Bu), 1.83 (t, 1 H,  $J = 12.5$  Hz,  $\text{CH}_\alpha\text{CH}_\text{A}\text{CHOH}$ ), 2.23-2.35 (m, 1 H,  $\text{CH}_\alpha\text{CH}_\text{B}\text{CHOH}$ ), 2.92-3.09 (m, 2H,  $\text{NCH}_2\text{CHOH}$ ), 3.31-3.34 (d, 1 H,  $J = 5.0$  Hz,  $\text{NCH}_2\text{CHOH}$ ), 4.12 (bs, 1 H,  $\text{CHCH}_2\text{CHOH}$ ), 4.48 (d, 1 H,  $J = 15.0$  Hz,  $\text{NCH}_\text{A}\text{Ph}$ ), 4.75 (d, 1 H,  $J = 14.5$  Hz,  $\text{NCH}_\text{B}\text{Ph}$ ), 4.84-4.87 (m, 1 H,  $\text{NHCH}_\alpha\text{CH}_2$ ), 6.06 (bd,  $J = 5.5$  Hz, 1 H, NH), 7.16-7.34 (m, 5H, Ar).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  28.3 (*t*-Bu), 38.7 ( $\text{CH}_\alpha\text{CH}_2\text{CH}$ ), 46.1 ( $\text{NCH}_2\text{CH}$ ), 51.7 ( $\text{CH}_\alpha$ ), 68.1 ( $\text{NCH}_2\text{Ph}$ ), 68.4 ( $\text{CCH}_2\text{CHOH}$ ), 69.9 ( $\text{NCH}_2\text{CHOH}$ ), 79.9 ( $\text{C}(\text{CH}_3)_3$ ), 127.8, 128.2, 128.7, 136.6 (Ar), 167.8 (OCO), 172.7 (NCO).

**(*S*)-benzyl 2-((2*R*, 3*R*)-2-(*tert*-butyloxycarbonyl)-3-phenylpent-4-enamido)propanoate (7.38a)**



7.38a

EDCI (66 mg, 0.34 mmol), HOBT (92 mg, 0.68 mmol) and NMP (10  $\mu\text{L}$ , 1.03 mmol) were added to a solution of the acid 7.37 (100 mg, 0.34 mmol) and (*S*)-alanine benzyl ester hydrochloride (73 mg, 0.34 mmol), using the general procedure M. The crude mixture

containing **7.38a** by  $^1\text{H}$  NMR < 10% of a second diastereoisomer tentatively assigned as the epimer **7.38b** of the acid, which was Purified by column chromatography (PE/EA = 85/15) to give 90 mg(58%) of **7.38a** as a white solid.

Data for **7.38a**:

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.30 (d,  $J = 7$  Hz,  $\text{CH}_3\text{NH}_\alpha$ ), 1.39 (3  $\text{CH}_3$ , *t*-Bu), 3.98 (t,  $J = 6.5$  Hz, 1H, PhCH), 4.46 (m, 1H,  $\text{PhCHCH}_\alpha\text{NH}$ ), 4.51-4.56 (m, 1H,  $\text{CH}_3\text{CH}_\alpha$ ), 4.96 (bd,  $J = 6$  Hz, 1H,  $\text{PhCHCH}_\alpha\text{NH}$ ), 5.14-5.19 (m, 4H,  $\text{PhCHCHCH}_2$ ,  $\text{CO}_2\text{CH}_2\text{Ph}$ ), 6.04-6.11 (m, 1H,  $\text{PhCHCHCH}_2$ ), 6.26 (d,  $J = 7.5$  Hz,  $\text{PhCHCH}_\alpha\text{NH}$ ), 7.22-7.39 (m, 10H, Ar).

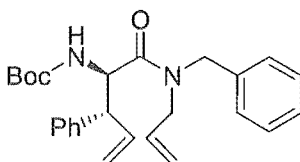
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  18.3 ( $\text{CH}_3\text{CH}_\alpha$ ), 28.2 (*t*-Bu), 48.2 ( $\text{CH}_3\text{CH}_\alpha$ ), 51.1 (PhCH), 58.2 ( $\text{NHCH}_\alpha\text{CHPh}$ ), 67.1 ( $\text{OCH}_2\text{Ph}$ ), 80.2 ( $\text{C}(\text{CH}_3)_2$ ), 118.1 ( $\text{PhCHCHCH}_2$ ), 127.2, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 130.9 (Ar), 136.0 ( $\text{PhCHCHCH}_2$ ), 139.1 (Ar), 155.3 ( $\text{OCO } t\text{-Bu}$ ), 169.8 ( $\text{OCOBn}$ ), 172.2 (NCO).

TOF MS  $\text{ES}^+$   $[\text{MH}]^+$ : Found: 451.2437; Calcd for  $\text{C}_{27}\text{H}_{35}\text{N}_2\text{O}_4$ : 451.2597.

Data for **7.38b**:

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.27 (d,  $J = 10$  Hz,  $\text{CH}_3\text{NH}_\alpha$ ), 1.38 (3  $\text{CH}_3$ , *t*-Bu), 3.94-3.99 (m, 1H, PhCH), 4.48 (bm, 1H,  $\text{PhCHCH}_\alpha\text{NH}$ ), 4.54 (t,  $J = 7$  Hz, 1H,  $\text{CH}_3\text{CH}_\alpha$ ), 5.06 (bd,  $J = 6$  Hz, 1H,  $\text{PhCHCH}_\alpha\text{NH}$ ), 5.13-5.41 (m, 4H,  $\text{PhCHCHCH}_2$ ,  $\text{CO}_2\text{CH}_2\text{Ph}$ ), 6.04-6.11 (m, 1H,  $\text{PhCHCHCH}_2$ ), 6.23 (bs, 1H,  $\text{PhCHCH}_\alpha\text{NH}$ ), 7.20-7.38 (m, 10H, Ar).

***tert*-Butyl ((1*R*, 2*S*)-1-[[allyl(benzyl)amino]carbonyl]-2-methylbut-3-en-1-yl) carbamate (7.39)**



EDCI (200 mg, 1.03 mmol), HOBt (334 mg, 2.47 mmol), NEM (258 mg, 2.06 mmol) and *N*-allyl benzyl amine **7.28** (2.06 mg, 5.80 mmol) were added to a solution of the acid **7.37**

(300 mg, 1.03 mmol) in DCM (30 mL) under argon with stirring at rt for 72 h according to the general procedure M. The crude product was purified by flash column chromatography (PE/EA = 90/10→85/15) to give 183 mg [44%, 2:1 (based on analysis of  $^1\text{H}$  NMR spectrum)] of the desired diene **7.39** as a white solid.

Data for (2:1) rotameric mixture.

FTIR(KBr): 3319, 2977, 2360, 1710, 1697, 1647, 1496, 1434, 1367, 1249, 1168, 1047, 921, 700.

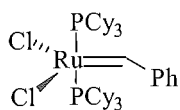
$^1\text{H}$ NMR (500 MHz)  $^1\text{H}$  NMR (500 MHz)  $\delta$  1.28 (s, 9H, *t*-Bu, minor), 1.30 (s, 9H, *t*-Bu, major), 3.66-3.76 (m, 2H,  $\text{CH}_\alpha\text{PhCH}$ , minor,  $\text{NCH}_\text{A}\text{CH}$ , minor), 3.80 (t, 1H,  $\text{CH}_\alpha\text{PhCH}$  major), 3.88 (dd,  $J = 16.5$  Hz, 6.0 Hz, 1H,  $\text{NCH}_\text{A}\text{CH}$ , major), 4.18 (dd,  $J = 15$  Hz, 6.0 Hz, 2H,  $\text{NCH}_\text{B}\text{CH}$ , major), 4.33-4.37 (m, 1H,  $\text{NCH}_\text{A}\text{Ph}$ , major and minor), 4.49 (d,  $J = 16.5$  Hz, 1H,  $\text{NCH}_\text{B}\text{Ph}$ , minor), 4.75 (d,  $J = 16.5$  Hz, 1H,  $\text{NCH}_\text{B}\text{Ph}$ , major), 4.75-4.78 (m, 1H,  $\text{NCH}_\text{B}\text{CH}$ , minor), 4.94 (t,  $J = 9$  Hz,  $\text{CH}_\alpha\text{PhCH}$ , major), 5.04 (t,  $J = 9$  Hz,  $\text{CH}_\alpha\text{PhCH}$ , minor), 5.08-5.20 (m, 4H,  $\text{PhCHCHCH}_2$ ,  $\text{NCH}_2\text{CHCH}_2$ , major and minor), 5.63-5.77 (m, 1H,  $\text{NCH}_2\text{CHCH}_2$ , major and minor), 5.92-6.90 (m, 1H,  $\text{PhCHCHCH}_2$ , minor), 6.06-6.13 (m, 1H,  $\text{PhCHCHCH}_2$ , major), 7.16-7.34 (m, 10H, major and minor).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  28.1, 28.3, 47.9, 48.3, 49.2, 50.0, 53.1, 53.2, 53.7, 53.7, 79.6, 117.7, 117.9, 126.9, 127.2, 127.4, 127.6, 128.4, 128.5, 128.6, 132.4, 132.7, 136.3, 136.6, 136.7, 136.9, 139.4, 139.4, 154.7, 154.8, 171.3, 171.5.

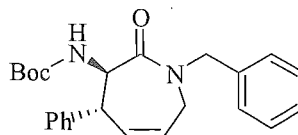
$[\alpha]^{20}_{\text{D}} +50.0$  (*c* 1.0  $\text{CHCl}_3$ )

TOF MS  $\text{ES}^+$   $[\text{MH}]^+$ : Found: 421.2498; Calcd for  $\text{C}_{26}\text{H}_{33}\text{N}_2\text{O}_3$ : 421.2491.

***tert*-Butyl [(3*R*,4*S*)-1-benzyl-4-phenyl-2-oxo-2,3,4,7-tetrahydro-1*H*-azepin-3-yl] carbamate (**7.40**)**



6.2





Catalyst **6.2** (68.5 mg, 0.08 mmol), dissolved in dry degassed DCM (3 mL) was added to solution of the diene **7.39** (175 mg, 0.42 mmol), dissolved in dry degassed DCM (20 mL) under argon, according to the general procedure O. The mixture was refluxed for 24 h. The crude product was purified by flash column chromatography (PE/EA = 8/2 ) to give 139 mg (85%) of the desired olefinic lactam **7.40** as a white crystalline solid.

FTIR(KBr): 3315, 2976, 2929, 1701, 1641, 1535, 1492, 1444, 1365, 1340, 1319, 1170, 1056, 1018, 937, 698.

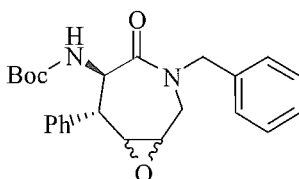
$^1\text{H}$  NMR (500 MHz)  $\delta$  1.10 (s, 9H, *t*-Bu), 3.36 (dd,  $J$  = 18.0 Hz, 8.0 Hz, 1H, PhCHCH), 3.42 (d,  $J$  = 11.5 Hz, 1H, NCH<sub>2</sub>CH), 4.45 (d, 1H,  $J$  = 17 Hz, NCH<sub>2</sub>CH), 4.62 (s, 2H, NCH<sub>2</sub>Ph), 5.16 (t, 1H,  $J$  = 10.5 Hz, NHCH <sub>$\alpha$</sub> ), 5.41 (d, 1H,  $J$  = 9 Hz, NHCH <sub>$\alpha$</sub> ), 5.64-5.67 (bm, 1H, CH<sub>2</sub>CHCH), 5.70-5.74 (m, 1H, PhCHCH), 7.12-7.27 (m, 10 H, Ar).

$^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  27.8 (C(CH<sub>3</sub>)<sub>3</sub>), 44.6 (NCH<sub>2</sub>CH), 49.4 (PhCHCH), 51.4 (NCH<sub>2</sub>Ph), 53.7 (NHCH), 79.0 (C(CH<sub>3</sub>)<sub>3</sub>), 124.4 (CH<sub>2</sub>CHCH), 126.9, 127.5, 127.9, 128.1, 128.58, 129.2 (Ar), 134.5 (PhCHCH), 136.6, 140.1 (Ar), 154.6 (OCO-*t*-Bu), 172.1 (NCO);

Anal found: C = 73.23, H = 7.36, N = 7.05; calcd: C = 73.44, H = 7.19, N = 7.13.

TOF MS ES<sup>+</sup> [MH]<sup>+</sup>: Found: 393.2204; Calcd for C<sub>24</sub>H<sub>29</sub>N<sub>2</sub>O<sub>3</sub>: 393.2178.

***tert*-Butyl [(5*R*,6*R*)-3-benzyl-6-phenyl-4-oxo-8-oxa-3- azabicyclo-[5.1.0]oct-5-yl] carbamate (**7.41**)**



The olefinic lactam **7.40** (40 mg, 0.10 mmol) in acetone (6 mL) and water (5 mL) was treated with sodium hydrogen carbonate (291 mg, 3.46 mmol) and Oxone® (627 mg, 1.02 mmol) as described in the general procedure P. The resulting crude epoxide was purified by

column chromatography (PE/EA = 70:30) to give 36 mg (87%) of **7.41** (5:4, based on analysis of  $^1\text{H}$  NMR spectrum) as a white solid.

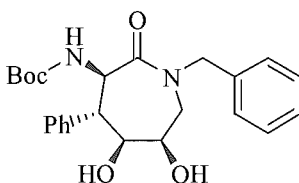
Data for mixture of isomers (5:4)

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.16 (s, 9H, *t*-Bu, major), 1.26 (s, 9H, *t*-Bu, minor), 3.00-3.28 (m, 3H,  $\text{NCH}_2\text{CHCH}$ , major & minor,  $\text{PhCHCH}$ , major & minor,  $\text{PhCH}$ , major), 3.69-3.76 (m, 1H,  $\text{NCH}_\text{A}\text{CH}$ , major & minor), 3.94 (dd, 1H,  $J = 15.5$  Hz, 5 Hz,  $\text{PhCH}$ , 1H minor), 4.00 (d,  $J = 15.0$  Hz, 1H,  $\text{NCH}_\text{A}\text{Ph}$ , major), 4.22 (d,  $J = 16.5$  Hz, 1H,  $\text{NCH}_\text{B}\text{CH}$ , major & minor), 4.34 (d,  $J = 15$  Hz, 1H,  $\text{NCH}_\text{A}\text{Ph}$ , minor), 4.82-4.90 (m, 1H,  $\text{CH}_\alpha\text{CHPh}$ , major & minor), 5.05 (d,  $J = 14$  Hz, 1H,  $\text{NCH}_\text{B}\text{Ph}$ , minor), 5.24 (d,  $J = 10$  Hz, 1H,  $\text{NH}$ , minor), 5.33 (d,  $J = 15.5$  Hz, 1H,  $\text{NCH}_\text{B}\text{Ph}$ , major), 5.41 (d,  $J = 9$  Hz, 1H,  $\text{NH}$ , major), 7.26-7.53 (m, 10 H, Ar, major & minor).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  28.0, 29.7, 43.9, 47.3, 47.6, 50.4, 51.3, 52.1, 52.2, 54.5, 56.4, 57.0, 68.4, 79.3, 80.4, 127.3, 127.7, 128.5, 128.7, 129.0, 129.6, 136.2, 136.9, 139.3, 154.6, 155.2, 169.4, 171.4.

TOF MS  $\text{ES}^+$   $[\text{M}+\text{H}]^+$ : Found: 409.2124; Calcd for  $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_4$ : 409.2127.

***tert*-Butyl [(3*R*,4*R*,5*S*,6*R*)-1-benzyl-5,6-dihydroxy-4-phenyl-2-oxoazepan-3-yl]-carbamate (**7.42**)**



Potassium osmate (2.2 mg, 0.003 mmol), olefinic lactam **7.40** (25 mg, 0.06 mmol), *t*-butyl alcohol (3 mL), water (3 mL), potassium carbonate (26 mg, 0.19 mmol), potassium ferricyanide (63 mg, 0.19), ligand **7.21** or **7.22** (2.5 mg, 0.0003 mmol) and methane sulphonamide (12 mg, 0.13 mmol) were reacted according to the general method Q with stirring for 48 h. The crude product (obtained as a single isomer, determined by analysis of

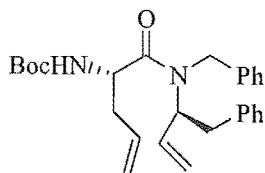
$^1\text{H}$  NMR spectrum) was purified by flash column chromatography (PE/EA = 1/1  $\rightarrow$  20/80) to give 14 mg (51%) of **7.42** (14 mg, 51%) as a colorless oil, along with recovered 9 mg (36%) of **7.40**.

$^1\text{H}$ NMR (500 MHz)  $\delta$  1.21 (s, 9H, *t*-Bu), 1.70 (bs, 1H, ( NCH<sub>2</sub>CHCHOH ), 1.90 (bs, 0.5 H, CH<sub>2</sub>CHCHOH), 2.74 (bs, 0.5 H, CH<sub>2</sub>CHCHOH), 3.09 (t, *J* = 10 Hz, 1H, CH<sub>α</sub>CHPh), 3.56 (dd, *J* = 16.5 Hz, 6.0 Hz, 1H, NCH<sub>A</sub>CH), 3.67 (m, 1H, , NCH<sub>B</sub>CH), 4.02 (d, *J* = 15 Hz, 1H, NCH<sub>A</sub>Ph), 4.07 (dd, *J* = 11 Hz, 3.5 Hz, 1H, PhCHCHOH), 4.16 (d, *J* = 6 Hz, 3.5 Hz, 1H, CH<sub>2</sub>CHCHOH ), 4.76 (t, *J* = 9.5 Hz, 1H, CH<sub>α</sub>), 5.43 (d, *J* = 9 Hz, 1H, NH), 5.59 (d, *J* = 14.5 Hz, 1H, NCH<sub>B</sub>Ph ), 7.27-7.36 (m, 10 H, Ar).

$^{13}\text{C}$ NMR (75 MHz)  $\delta$  28.11 (3 CH<sub>3</sub>), 46.39 (NCH<sub>2</sub>CH), 49.82 (CH<sub>α</sub>CHPh), 51.29 (CH<sub>α</sub>), 53.03 (NCH<sub>2</sub>Ph), 68.48 (NCH<sub>2</sub>CHOH), 76.66 (CH<sub>2</sub>CHCHOH), 79.32 (C(CH<sub>3</sub>)<sub>3</sub>), 127.56, 127.76, 128.24, 128.67, 128.71, 136.60, 136.88 (Ar), 155.09 (OCO), 171.81 (NCO)

TOF MS ES<sup>+</sup> [MH]<sup>+</sup>: Found: 427.2309; Calcd for C<sub>24</sub>H<sub>31</sub>N<sub>2</sub>O<sub>5</sub>: 427.2233.

***tert*-Butyl ((1*S*)-1-({benzyl[(1*S*)-1-benzylprop-2-en-1-yl]amino}carbonyl) but-3-en-1-yl carbamate (**7.47**)**



(*S*)-*N*-Boc allyl glycine (250 mg, 1.16 mmol), Bop coupling reagent (513 mg  $\times$  5, 1.16 mmol) and DIPEA (620  $\mu\text{L}$ , 3.48 mmol) were added to a solution of the amine **7.46** (275 mg, 1.16 mmol) in DCM (20 mL) under argon according to the general procedure N with stirring at rt for 72 h. The crude residue (3:2, based on analysis of  $^1\text{H}$  NMR spectrum) was purified by flash column chromatography (PE/EA = 9/1) to give 336 mg (67%) of **7.47** (3:2) as a clear oil.

Data for **7.47** (3:2 mixture)

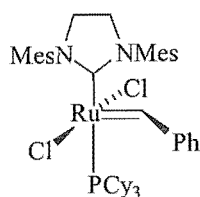
FTIR (KBr): 2977, 2856, 2360, 1697, 1647, 1633, 1497, 1434, 1367, 1249, 1168, 1047, 921, 700.

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.42 (s, 9H, *t*-Bu, major), 1.43 (s, 9H, *t*-Bu, minor), 1.96-2.00 (m,  $\text{CH}_\alpha\text{CH}_\text{A}\text{CH}$ , 1H, major), 2.13-2.17 (m,  $\text{CH}_\alpha\text{CH}_\text{B}\text{CH}$ , 1H, major), 2.21 (t,  $J = 7.0$  Hz, 1H,  $\text{CHCH}_\text{A}\text{Ph}$ , major), 2.72-2.75 (m,  $\text{CH}_\alpha\text{CH}_\text{A}\text{CH}$ , 1H, minor), 2.84-2.85 (m,  $\text{CH}_\alpha\text{CH}_\text{B}\text{CH}$ , 1H, minor), 2.89 (dd,  $J = 13.5$  Hz, 7.0 Hz, 1H,  $\text{CHCH}_\text{B}\text{Ph}$ , major), 2.94 (d,  $J = 7.5$  Hz, 1H,  $\text{CHCH}_\text{A}\text{Ph}$ , minor), 3.01 (dd,  $J = 13.5$  Hz, 7.0 Hz, 1H,  $\text{CHCH}_\text{B}\text{Ph}$ , minor), 4.26 (d,  $J = 15$  Hz, 1H,  $\text{NCH}_\text{A}\text{Ph}$ , major), 4.42-4.51 (m, 3H,  $\text{NCH}_\text{A}\text{Ph}$ , minor,  $\text{CHCH}_2\text{Ph}$ , major), 4.51-4.60 (m, 1H,  $\text{CHCH}_2\text{Ph}$ , minor), 4.83 (d,  $J = 16$  Hz,  $\text{NCH}_\text{B}\text{Ph}$ , major), 4.85-4.87 (m, 1H,  $\text{NHCH}_\alpha$ , major & minor), 4.95-5.31 (m, 5H,  $\text{NCHCHCH}_2$ ,  $\text{CHCH}_2\text{CHCH}_2$ , major & minor,  $\text{NCH}_\text{B}\text{Ph}$ , minor), 5.53-5.63 (m, 1H,  $\text{NCHCHCH}_2$ , major), 5.76-5.87 (m, 2H,  $\text{NCHCHCH}_2\text{CHCH}_2$ , minor), 5.94-6.01 (m, 1H,  $\text{CH}_2\text{CHCH}_2$ , major), 7.05 (d,  $J = 7.0$  Hz, 1H, Ar), 7.14-7.29 (m, Ar, major & minor).

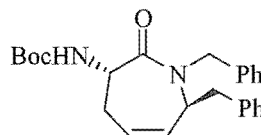
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  28.3 (*t*-Bu, major), 29.6 (*t*-Bu, minor), 37.3 ( $\text{CH}_\alpha\text{CH}_2\text{CH}$ , minor), 37.6 ( $\text{CHCH}_2\text{Ph}$ , major), 38.4 ( $\text{CH}_\alpha\text{CH}_2\text{CH}$ , major), 38.6 ( $\text{CHCH}_2\text{Ph}$ , minor), 46.5 ( $\text{NCH}_2\text{Ph}$ , minor), 49.7 ( $\text{NCH}_2\text{Ph}$ , major and  $\text{CH}_\alpha$ , minor), 50.7 ( $\text{CH}_\alpha$ , major), 60.9 ( $\text{CHCH}_2\text{Ph}$ , major), 61.1 ( $\text{CHCH}_2\text{Ph}$ , minor), 79.5 ( $\text{C}(\text{CH}_3)_3$ , major), 79.6 ( $\text{C}(\text{CH}_3)_3$ , minor), 117.6, 118.0 ( $\text{CH}_2\text{CHCH}_2$ , major and minor), 118.1, 118.2 ( $\text{CH}_2\text{CHCH}$ , major & minor), 126.4, 126.7, 126.8, 127.0, 127.3, 127.5, 128.3, 128.6, 128.7, 129.3 (Ar, major & minor), 133.0, 133.2 ( $\text{CH}_2\text{CHCH}$ , major), 135.7, 136.2 ( $\text{CH}_2\text{CHCH}_2$ , major and minor), 137.1, 137.4, 138.1, 138.4 (Ar), 155.1, 155.2 ( $\text{OCO}t\text{-Bu}$ , major & minor), 172.7, 172.9 ( $\text{NCO}$ , major and minor);  $[\alpha]^{20}_{\text{D}} -66.2$  (c 1.0  $\text{CHCl}_3$ ).

TOF MS  $\text{ES}^+$   $[\text{MH}]^+$ : Found: 435.2635; Calcd for  $\text{C}_{27}\text{H}_{35}\text{N}_2\text{O}_3$ : 435.2648.

***tert*-Butyl [(3*S*,7*S*)-1-benzyl-7-benzyl-2-oxo-2,3,4,7-tetrahydro-1*H*-azepin-3-yl]  
carbamate (**7.48**)**



**6.4**



Catalyst **6.4** (46 mg, 0.05 mmol), dissolved in dry degassed DCM (3 mL) was added to solution of the diene **7.47** (291 mg, 0.67 mmol), dissolved in dry degassed DCM (20 mL) under argon, according to the general procedure O. The mixture was refluxed for 36 h. The crude product was purified by flash column chromatography (PE/EA = 9/1 then 8/2 ) to give 250 mg (92%) of the desired olefinic lactam **7.48** as a brown oil.

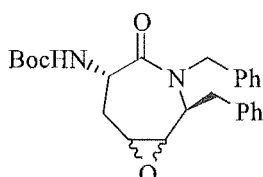
IR (KBr): 3062, 2977, 1737, 1649, 1458, 1471, 1440, 1365, 1325, 1172, 1055, 1029, 985, 871, 702.

<sup>1</sup>H NMR (500 MHz)  $\delta$  1.48 (s, 9H, *t*-Bu), 2.30 (dt,  $J$  = 14.5 Hz, 2 Hz, 1H, NHCHCH<sub>2</sub>), 2.66 (dd,  $J$  = 18 Hz, 4 Hz, 1H, NHCHCH<sub>2</sub>), 3.03-3.11 (m, 2H, CHCH<sub>2</sub>Ph), 3.56 (d,  $J$  = 15.5 Hz, 1H, NCH<sub>A</sub>Ph), 3.92 (dd,  $J$  = 14 Hz, 6.5 Hz, 1H, CHCH<sub>2</sub>Ph), 4.82-4.86 (m, 1H, NHCH <sub>$\alpha$</sub> ), 5.07 (d,  $J$  = 15 Hz, 1H, NCH<sub>B</sub>Ph), 5.46 (t,  $J$  = 10 Hz, 1H, NCHCH), 5.77 (dd,  $J$  = 11.5 Hz, 6 Hz, 1H, CH <sub>$\alpha$</sub> CH<sub>2</sub>CH), 6.03 (bd,  $J$  = 6.5 Hz, 1H, NHCH <sub>$\alpha$</sub> ), 7.09-7.15 (m, 2H, Ar), 7.23-7.35 (m, 3H, Ar).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  28.4 (*t*-Bu), 32.5 (NHCHCH<sub>2</sub>), 42.4 (CHCH<sub>2</sub>Ph), 52.3 (NCH<sub>2</sub>Ph), 52.4 (NHCH <sub>$\alpha$</sub> ), 61.4 (CHCH<sub>2</sub>Ph), 79.5 (C(CH<sub>3</sub>)<sub>3</sub>), 126.9 (CH <sub>$\alpha$</sub> CH<sub>2</sub>CH), 127.4, 127.4, 127.5, 128.2 (NCHCH), 128.6, 128.6, 129.1, 136.9, 137.5 (Ar), 155.1 (OCO<sup>*t*</sup>-Bu), 172.1 (NCO);  $[\alpha]_D^{20}$  -29.8 (c 1.0 CHCl<sub>3</sub>).

TOF MS ES<sup>+</sup> [MH]<sup>+</sup>: Found: 429.2157; Calcd for C<sub>25</sub>H<sub>31</sub>N<sub>2</sub>NaO<sub>3</sub>: 429.2154.

***tert*-Butyl [(2*S*,5*S*)-3-benzyl-2-benzyl-4-oxo-8-oxa-3-azabicyclo [5,1,0]oct-5-yl] carbamate (7.49)**



The olefinic lactam (80 mg, 0.197 mmol) in acetone (12 mL) and water (10 mL) was treated with sodium hydrogen carbonate (562 mg, 6.70 mmol) and Oxone® (1.21 g, 1.97 mmol) as described in the general procedure P. The resulting crude epoxide (~1:1, based on analysis of <sup>1</sup>H NMR spectrum) was purified by column chromatography (PE/EA = 70/30) to give 70 mg (84%) of **7.49** (~1:1) as a white foam.

Data for mixture of diastereomers: (~1:1)

FTIR (KBr): 3030, 2972, 2979, 2856, 2360, 2343, 1708, 1645, 1602, 1542, 1473, 1440, 1365, 1240, 1166, 1053, 1028, 941, 869, 736, 698.

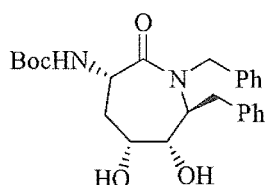
<sup>1</sup>H NMR (500 MHz) δ 1.45 (s, 9H, *t*-Bu), 2.01 (d, *J* = 14.5 Hz, 1H, CHCH<sub>A</sub>CH), 2.09 (d, *J* = 13.0 Hz, 1H, CHCH<sub>A</sub>CH), 2.55 (m, 1H, CHCH<sub>B</sub>CH), 2.69 (d, *J* = 14.5 Hz, 1H, CHCH<sub>B</sub>CH), 2.89-2.93 (m, 2H, CHCH<sub>AB</sub>Ph), 2.98 (dd, *J* = 13 Hz, 6 Hz, 1H, OCHCHN), 3.11 (dd, *J* = 7.5 Hz, 4 Hz, 1H, OCHCH<sub>2</sub>CH), 3.17 (dd, *J* = 14 Hz, 8 Hz, 1H, OCHCH<sub>2</sub>CH), 3.27 (bm, 1H, OCHCHN), 3.30 (t, *J* = 5 Hz, 2H, CHCH<sub>AB</sub>Ph), 3.63 (d, *J* = 14.5 Hz, 1H, NCH<sub>A</sub>Ph), 3.92 (dd, *J* = 14.5 Hz, 7 Hz, 1H, CHCHN), 4.11 (m, 1H, CHCHN), 4.40 (s, 2H, NCH<sub>AB</sub>Ph), 4.55 (t, *J* = 9 Hz 1H, NHCH), 4.62 (m, 1H, NHCH), 5.05 (d, *J* = 15 Hz, 1H, NCH<sub>B</sub>Ph), 5.79 (bd, *J* = 6.5 Hz, 1H, NH), 5.97 (bd, *J* = 6.5 Hz, 1H, NH), 6.92 (d, *J* = 7.5 Hz, 2H, Ar), 7.14 (d, *J* = 7.5 Hz, 2H, Ar), 7.18 (d, *J* = 7.5 Hz, 2H, Ar), 7.22-7.36 (m, 4H, Ar).

<sup>13</sup>C NMR (75 MHz) δ 28.4 (C(CH<sub>3</sub>)<sub>3</sub>), 29.8, 32.2 (CHCH<sub>2</sub>CH), 37.5, 38.6 (CHCH<sub>2</sub>Ph), 46.9, 50.6 (NHCH), 52.4, 53.1 (NCH<sub>2</sub>Ph), 53.3, 53.7 (CHCHCH<sub>2</sub>Ph), 54.8, 55.3 (CHCH<sub>2</sub>CH), 58.8, 58.9, (CHCH<sub>2</sub>Ph), 79.8, 80.4 (C(CH<sub>3</sub>)<sub>3</sub>), 126.9, 127.1, 127.8, 127.9,

128.5, 128.7, 128.9, 129.0, 129.3, 136.2, 137.0, 137.2, 137.5 (Ar), 155.0 (OCO'-Bu), 171.2, 172.2 (NCO).

TOF MS ES<sup>+</sup> [MH]<sup>+</sup>: Found: 423.2284; Calcd for C<sub>25</sub>H<sub>31</sub>N<sub>2</sub>O<sub>4</sub>: 423.2284.

***tert*-Butyl[(3*S*,5*R*,6*S*,7*S*)-1-benzyl-5,6-dihydroxy-7-benzyl-2-oxoazepan-3-yl] carbamate (7.50)**



(a) Potassium osmate (2mg, 0.005 mmol), olefinic lactam **7.48** (20 mg, 0.05 mmol), *t*-butyl alcohol (3 mL), water (3 mL), potassium carbonate (21 mg, 0.15 mmol), potassium ferricyanide (49 mg, 0.15), ligand **7.21** or **7.22** (4 mg, .002 mmol) and methane sulphonamide (10 mg, 0.1 mmol) were reacted according to the general method Q with stirring for 48h. The crude product **7.50** (obtained as a single diastereoisomer, based on analysis of <sup>1</sup>H NMR spectrum) was purified by flash column chromatography (PE/EA = 50/50→ 20/80) to give 11 mg (52%) of **7.50** as a white oily solid.

<sup>1</sup>H NMR (CD<sub>3</sub>CN, 500 MHz) δ 1.30 (s, 9H, *t*-Bu), 1.64-1.74 (m, 2H, CHCH<sub>2</sub>CHOH), 2.49 (dd, *J* = 13.5 Hz, 6Hz, 1H, CHCH<sub>A</sub>Ph), 2.76 (bs, 1H, CHCHOH), 2.86 (dd, *J* = 13.5 Hz, 10 Hz, 1H, CHCH<sub>B</sub>Ph), 2.99 (bs, 1H, CH<sub>2</sub>CHOH), 3.51 (bs, 1H, CHCHOH), 3.61-3.66 (m, 1H, CHCHOH), 3.96 (d, *J* = 14.5 Hz, 1H, NCH<sub>A</sub>Ph), 4.01-4.03 (m, 1H, CH<sub>2</sub>CHOH), 4.15-4.18 (m, 1H, CHCH<sub>2</sub>CHOH), 4.69 (d, *J* = 14.5 Hz, 1H, NCH<sub>B</sub>Ph), 5.82 (bs, 1H, NH), 6.77 (d, *J* = 7.0 Hz, 2H, Ar), 7.02-7.09 (m, 3H, Ar), 7.13-7.19 (m, 5H, Ar).

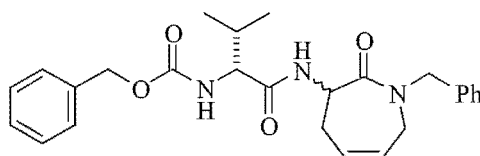
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 28.43 (*t*-Bu), 33.98 (CH<sub>α</sub>CH<sub>2</sub>CH), 37.16 (NCHCH<sub>2</sub>Ph), 50.04 (CH<sub>α</sub>CH<sub>2</sub>CH), 54.79 (NCH<sub>2</sub>Ph), 63.41 (NCHCHOH), 68.64 (CH<sub>2</sub>CHOH), 69.69 (CHCHOH), 79.83 (C(CH<sub>3</sub>)<sub>2</sub>), 127.0, 128.0, 128.55, 128.79, 128.84, 129.21, 137.06, 137.33 (Ar), 155.21 (CO<sub>2</sub>*t*-Bu), 171.44 (NCO); [α]<sub>D</sub><sup>20</sup> +18.1 (*c* 1.0 CHCl<sub>3</sub>).

TOF MS ES<sup>+</sup> [MH]<sup>+</sup>: Found: 441.2389; Calcd for C<sub>25</sub>H<sub>33</sub>N<sub>2</sub>O<sub>5</sub>: 441.2389.

(b) Potassium osmate (2mg, 0.005 mmol), olefinic lactam **7.48** (20 mg, 0.05 mmol), *t*-butyl alcohol (3 mL), water (3 mL), potassium carbonate (21 mg, 0.15 mmol), potassium ferricyanide (49 mg, 0.15), and methane sulphonamide (10 mg, 0.1 mmol) were reacted according to modified general method Q in the absence of ligands with stirring for 48 h. The crude product **7.50** (obtained as a single diastereoisomer, based on analysis of <sup>1</sup>H NMR spectrum) was purified by flash column chromatography (PE/EA = 50/50 → 20/80) to give 12.5 mg (59%) of **7.50** as a white oily solid.

Data for **7.50** as above

**Benzyl (1 (RS)-{[(1-benzyl-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-yl)amino]carbonyl}-2(S)-methylpropyl)carbamate (7.57)**



Compound **7.30** (200 mg, 0.63 mmol) was treated with 1 N HCl (aqueous, 2 mL) in EA (6 mL) at rt with stirring for 4 h. The progress of the reaction was monitored by TLC. EA was evaporated in vacuo, MeOH was added (×2) and the solvent was evaporated in vacuo. The crude free amine **7.55** was dried in vacuo and used without further purification.

(*S*)-*N*,Cbz Valine (137 mg, 0.55 mmol) was added to the crude free amine **7.55** (118 mg, 0.55 mmol), EDCI (104 mg, 0.55 mmol), HOBT (147 mg, 1.09 mmol) and DIPEA (190 μL, 1.09 mmol) in dry DCM (20 mL) and the mixture was stirred at rt for 16 h. Water (4 mL) and EA (8 mL) were added to the mixture, the organic phase separated and the aq. phase extracted with EA (×3). The combined organic fractions were washed with H<sub>2</sub>O (×2),



NaHCO<sub>3</sub>, brine, dried (MgSO<sub>4</sub>) and evaporated in vacuo. The residue (a mixture of 1:1 diastereoisomers by analysis of <sup>1</sup>H NMR spectrum) was purified by flash column chromatography (PE/EA = 50:50) to give 160 mg (66%) of **7.56** (12 mg, 52%) as a white solid.

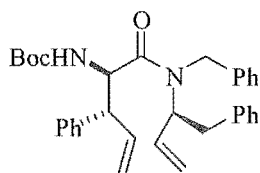
Data for **7.56** (1:1) mixture of diastereoisomers

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 0.92 (dd, *J* = 7 Hz, 2.5 Hz, 3H, (CH<sub>3</sub>)<sub>2</sub>CH), 0.98 (dd, *J* = 7 Hz, 2.5 Hz, 3H, (CH<sub>3</sub>)<sub>2</sub>C), 2.04-2.26 (m, 2H, (CH<sub>3</sub>)<sub>2</sub>CH, CH=CHCH<sub>A</sub>CH), 2.23-2.26 (m, 1H, CH=CHCH<sub>B</sub>CH), 3.34-3.39 (m, 1H, NCH<sub>A</sub>CH), 4.14 (dd, *J* = 13 Hz, 7 Hz, 1H, NHCH<sub>α</sub>CH<sub>2</sub>), 4.27-4.33 (m, 1H, CH=CHCH<sub>B</sub>CH), 4.60 (d, *J* = 14.5 Hz, 1H, NCH<sub>A</sub>Ph), 4.73 (d, *J* = 14.5 Hz, 1H, NCH<sub>B</sub>Ph), 5.08-5.21 (m, 3H, (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>α</sub>, PhCH<sub>2</sub>O), 5.43 (bm, 1H, NHCHCH<sub>2</sub>), 5.45-5.59 (m, 1H, CHCH<sub>2</sub>CH), 5.60-5.69 (m, 1H, NCH<sub>2</sub>CH), 7.20-7.36 (m, 10H, Ar)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 17.5, 17.6 (CH<sub>3</sub>), 19.1, 19.2 (CH<sub>3</sub>), 31.3, 31.4 ((CH<sub>3</sub>)<sub>2</sub>CH), 32.3, 32.5 (CHCH<sub>2</sub>CH), 45.1 (NCH<sub>2</sub>CH), 49.1 ((CH<sub>3</sub>)<sub>2</sub>CHCH<sub>α</sub>), 51.7 (NCH<sub>2</sub>Ph), 60.1, 60.2 (NHCH<sub>α</sub>CH<sub>2</sub>), 67.0 (PhCH<sub>2</sub>O), 124.1, 124.2 (NCH<sub>2</sub>CH), 127.6, 127.8, 128.0, 128.1, 128.5, 128.7 (Ar), 129.9 (CH<sub>2</sub>CHCH), 136.2, 136.5 (Ar), 156.3 (OCOBn), 170.1, 170.2 (NCO), 171.8, 171.9 (NHCO).

TOF MS ES<sup>+</sup> [MH]<sup>+</sup>: Found: 450.2394; Calcd for C<sub>26</sub>H<sub>32</sub>N<sub>3</sub>O<sub>4</sub>: 450.2393.

***tert*-Butyl ((1*R*, 2*S*)-1-({benzyl[(1*S*)-1-benzylprop-2-en-1-yl]amino}carbonyl)-2-phenylbut-3-en-1-yl)carbamate (**7.53**)**



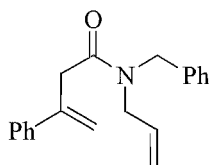
Pyridine (50 μL, 0.69 mmol) was added to a soln. of the acid **7.37** (200 mg, 0.69 mmol) in dry DCM (15 mL). The solution was cooled to -20 °C, cyanuric fluoride (500 μL, 3.43

mmol) was added and the mixture stirred for 2 h at the same temperature. DCM was evaporated in vacuo, dry toluene (20 mL) was added to the residue and filtered. The solvent was evaporated in vacuo and dried to give the acid fluoride **7.52** as a pale yellow oil which was used in the next step without purification.

To a solution of the amine **7.46** (150 mg, 0.63 mmol) in DCM (15 mL), was added DIPEA (60  $\mu$ L, 0.64 mmol) and stirred for 30 min at that temperature. A soln. of the crude **7.52** in DCM (5 mL) was added slowly to the reaction mixture and stirred for 2 h at 0 °C and 16 h at rt. Water was added to dilute the reaction mixture, organic layer was separated and aqueous layer back extracted with DCM ( $\times 3$ ). The combined organic extracts were washed with sat. NaHCO<sub>3</sub> soln and brine, dried (MgSO<sub>4</sub>) and evaporated in vacuo. The residue was purified by flash column chromatography to give 40 mg (12%) of **7.53** as a colourless viscous oil as well as 75 mg (50%) of the recovered amine **7.46**.

<sup>1</sup>H NMR(CDCl<sub>3</sub>, 500 MHz)  $\delta$  1.23, 1.25, 1.28, 1.33 (s, 9H), 2.81-2.86 (m, 1H), 2.90-2.98 (m, 2H), 3.16-3.20 (m, 0.5 H), 3.70-3.77 (m, 1H), 3.81-3.84 (m, 0.5 H), 4.08 (d,  $J$  = 17.5 Hz, 0.5 H), 4.36-4.55 (m, 1.5 H), 4.77-4.85 (m, 1H), 4.97-5.25 (m, 4H), 5.53-6.07 (m, 2H), 7.01-7.18 (m, 15 H).

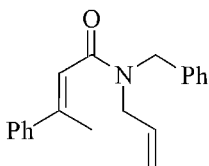
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  28.0, 28.0, 28.1, 28.1, 38.4, 38.5, 38.7, 39.6, 46.1, 48.5, 51.0, 53.2, 53.3, 53.6, 53.7, 54.0, 54.1, 55.5, 59.7, 61.0, 61.1, 62.9, 79.4, 79.5, 115.0, 117.3, 117.4, 117.5, 117.6, 117.8, 118.6, 126.2, 126.3, 126.5, 126.6, 126.7, 126.7, 126.8, 126.8, 126.9, 127.2, 127.3, 127.4, 127.4, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 128.4, 128.5, 128.6, 128.7, 128.7, 129.2, 129.3, 129.4, 135.6, 135.7, 135.8, 136.6, 136.7, 136.8, 137.0, 137.2, 137.6, 137.9, 138.2, 138.4, 138.5, 139.3, 139.5, 154.5, 171.8, 171.9.

***N*-allyl-*N*-benzyl-3-phenylbut-3-enamide (7.58)**

EDCI (279 mg, 1.45 mmol), HOBT (397 mg, 2.91 mmol) and NMP (420  $\mu$ L, 4.37 mmol) were added to a solution of the acid **7.57** (236 mg, 1.45 mmol) and *N*-allyl benzyl amine (213 mg, 1.45 mmol), using the general procedure M. The crude mixture containing **7.58** by  $^1\text{H}$  NMR 35% of a by product **7.59**, which was purified by column chromatography (PE/EA = 90/10) to give 150 mg of **7.58** (35%) as a colorless oil as well as **7.59** (15%) as a yellow oil.

Data for **7.58** (2:3)

$^1\text{H}$  NMR (acetone- $\text{d}_6$ , 500 MHz)  $\delta$  3.52 (s, 2H,  $\text{PhCCH}_2$ , minor), 3.56 (s, 2H,  $\text{PhCCH}_2$ , major), 3.83 (s, 2H,  $\text{NCH}_2\text{CH}$ , major), 3.86 (s, 2H,  $\text{NCH}_2\text{CH}$ , minor), 4.43 (s, 2H,  $\text{NCH}_2\text{Ph}$ , major), 4.49 (s, 2H,  $\text{NCH}_2\text{Ph}$ , minor), 4.97-5.14 (m, 3H,  $\text{NCH}_2\text{CHCH}_2$ ,  $\text{CH}_2\text{C(Ph)CH}_2$ , major and minor), 5.42-5.43 (m, 1H,  $\text{CH}_2\text{C(Ph)CH}_2$ , major and minor), 5.63-5.69 (m, 1H,  $\text{NCH}_2\text{CHCH}_2$ , minor), 5.70-5.79 (m, 1H,  $\text{NCH}_2\text{CHCH}_2$ , major), 6.8-7.4 (m, 10H, Ar).

**(2*E*)-*N*-allyl-*N*-benzyl-3-phenylbut-2-enamide (7.59)**

Data for **7.59** (~1:1)  $^1\text{H}$  NMR (acetone- $\text{d}_6$ , 500 MHz)  $\delta$  2.94, 2.51 (s, 3H,  $\text{CH}_3$ ), 4.15-4.25 (m, 2H,  $\text{NCH}_2\text{CH}$ ), 4.76-4.84 (m,  $\text{NCH}_2\text{Ph}$ ), 5.34-5.41 (m, 2H,  $\text{NCH}_2\text{CHCH}_2$ ), 5.97-6.11 (m, 1H,  $\text{NCH}_2\text{CHCH}_2$ ), 6.64 (s, 1H,  $\text{PhCCHCO}$ ), 7.44-7.75 (m, 10H, Ar).

## 8.7 References for Chapter Eight

1. Experimental work for chapters 3 and 5 was carried out at the Chemistry Department in the University of Tokyo, Japan using these general parameters:  $^1\text{H}$  NMR (500 MHz) and  $^{13}\text{C}$  NMR (125 MHz) spectra were recorded on Bruker Avance 500 and Bruker DRX 500 spectrometers in  $\text{CDCl}_3$  using TMS (for  $^1\text{H}$ :  $\delta = 0$ ) and  $\text{CDCl}_3$  (for  $^{13}\text{C}$ :  $\delta = 77.0$ ) as internal standard. IR spectra were recorded on a Horiba FT 300 spectrophotometer. High-resolution mass spectra were obtained with a JEOL JMS-700P mass spectrometer. Microanalyses were carried out at The Elemental Analysis Laboratory, Department of Chemistry, Faculty of Science, The University of Tokyo. The reagents were mainly purchased from Merck or Kanto Chemical Co., Inc.
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